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(54) GUANIDINOBENZOIC ACID ESTER COMPOUND

(57) [Problem]

To provide a compound which is useful as an agent for preventing and/or treating kidney diseases.

[Means for Solution]

The present inventors have studied compounds having a trypsin inhibitory activity, and have confirmed that a guanidinobenzoic acid ester compound has a trypsin inhibitory activity, thereby completing the present invention. The guanidinobenzoic acid ester compound of the present invention can be used as an agent for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like) as an agent which will substitute low-protein diet therapy, and/or as an agent for preventing and/or treating trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like).

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Description

Technical Field

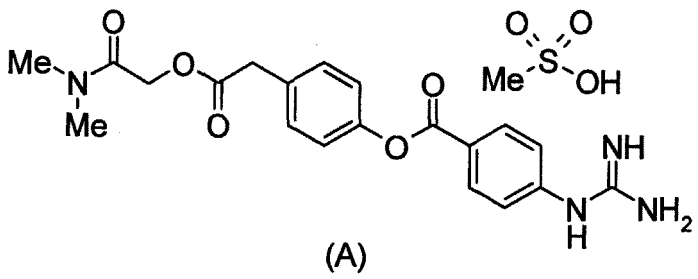
[0001] The present invention relates to a guanidinobenzoic acid ester compound which is useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for treating kidney diseases.

Background Art

[0002] Low-protein diet therapy for various kidney diseases (for example, chronic kidney diseases, acute glomerulonephritis, and acute kidney injury) has been practiced for a long time. Its mechanism of action has not still been clarified, but is thought to (1) reduce the total amount of the nitrogen compounds derived from protein, and decrease the glomerular loading, (2) suppress the production of uremic toxins derived from protein, which cause renal injury, (3) suppress the accumulation of phosphorous or potassium derived from protein, (4) suppress the production of acids derived from protein, and the like, by inhibiting the intake of the protein derived from diet. The effect of the low-protein diet therapy on inhibiting the progression of the kidney diseases has been proved in the clinical tests that have hitherto been conducted ((a) "The New England Journal of Medicine", 1989, Vol. 321, No. 26, pp. 1773-1777; and (b) "American Journal of Kidney Diseases", 2003, Vol. 41, No. 3, pp. S31-S34), and the intake amount of the protein for a patient with a kidney disease is also established in society guidelines (Japan Society of Nephrology, "Evidence-Based Clinical Practice Guideline for CKD 2013", 2013, pp. 25-30). On the other hand, the low-protein diet therapy has problems of a low extent of long-term strict practice due to necessity for technical knowledge, high cost, and low dietary compliance resulting from taste.

[0003] It is known that a compound which inhibits trypsin as one of serine proteases is useful for diseases involving this enzyme, such as pancreatitis and gastroesophageal reflux disease. Indeed, camostat mesylate (which will be hereinafter described Camostat) of the following Formula (A) which is a trypsin inhibitor (Patent Document 1) has been actually used for chronic pancreatitis and gastroesophageal reflux disease in clinical practice. Further, it has also been reported that Camostat has effects of inhibiting the urinary albumin excretion in animal models with diabetes mellitus ("Nephron", 1996, Vol. 74, No. 4, pp. 709-712), and reducing the amount of the urinary protein excretion in a variety of kidney diseases patients ("Clinical Nephrology", 1989, Vol. 32, p. 119-123).

[Chem. 1]

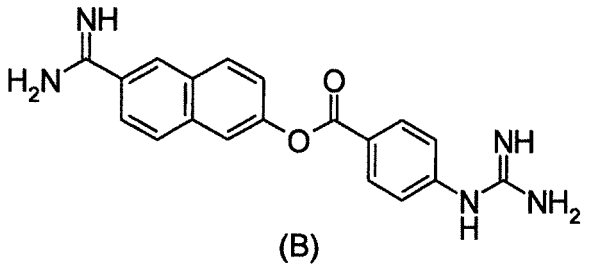


(A)

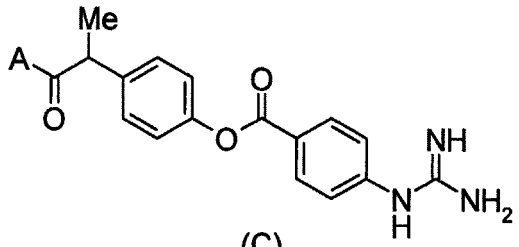
[0004] In addition, trypsin is involved in the proliferation of influenza viruses. For example, it is necessary that hemagglutinin (HA) on the virus surface should be cleaved into two subunits of HA1 and HA2 by the trypsin in the airway or mucosal intestinal epithelium in order to obtain the infectivity of the virus. It has been reported that by inhibition of the trypsin, the cleavage of this HA is suppressed and the virus loses infectivity, whereby the proliferation is suppressed. Therefore, a compound inhibits the trypsin can also be used as an anti-influenza drug ((a) "Antiviral Research", 2011, Vol. 92, No. 1, p. 27-36; (b) "Protease Groups of Individuals which Determine Susceptibility to Infection of Influenza Virus and Pathogenesis of Influenza-Associated Encephalopathy", "The Japanese Journal of Pharmacology", 2003, Vol. 122, p. 45-53).

[0005] As a compound exhibiting a trypsin inhibitory activity, other than Camostat, Compound (B) (Patent Document 2), Compound (C) (Patent Document 3), Compound (D) (Patent Document 4), Compound (E) (Patent Document 5), Compound (F) (Patent Document 6), Compound (G) (Patent Document 7), and Compound (H) (Patent Document 8) of the following formulae have been reported. However, there is no disclosure of the compound of the formula (I) or a salt thereof of the present application as described later in these documents.

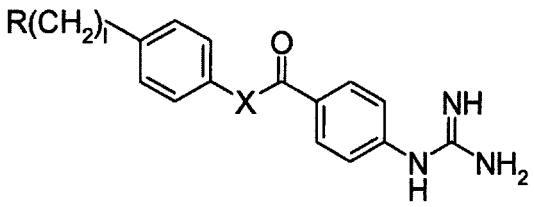
[Chem. 2]



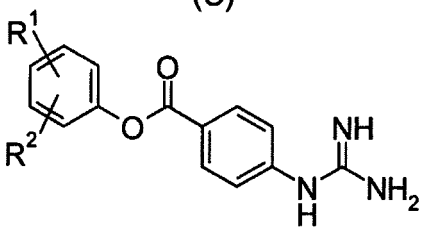
(B)



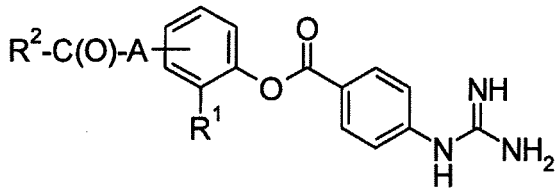
(C)



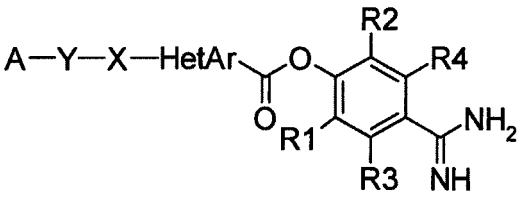
(D)



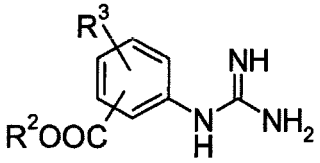
(E)



(F)



(G)

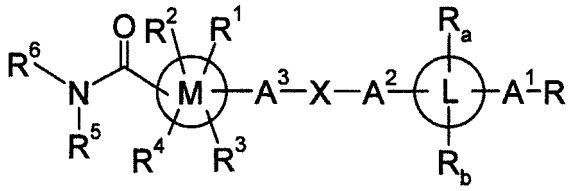


(H)

(In the formula (C), A is -N(R_1, R_2) or the like, and R_1 and R_2 are each H, lower alkyl having 1 to 8 carbon atoms, aralkyl which may have a substituent, or the like. In the formula (D), X is an oxygen atom or a sulfur atom, and R is -C(O)N(R^1)-$(CH_2)_m$-(1-azabicyclo[3.3.0]octan-5-yl) or the like. In the formula (E), R^1 is a hydrogen atom or a halogen atom, and R^2 is -$OCOR^3$ or the like. In the formula (F), A is $(-CH_2)_n$ or a styrene group, R^2 is -$NH(CH_2)_mCOOR^4$, -NHCH-(-R^5)-$COOR^4$, -NH-C_6H_4-$(CH_2)_p$-$COOR^4$, or the like, m is 2 or 3, p is an integer of 0 or 1, R^4 is a hydrogen atom, lower alkyl, or a substituted or unsubstituted benzyl group, R^5 is a substituted or unsubstituted benzyl group, a methoxycarbonylmethyl group, and the substituent of the substituted benzyl group means a halogen atom, a nitro group, a lower alkyl group, a hydroxy group, an alkoxy group having 2 to 6 carbon atoms, or the like. In the formula (G), X represents lower alkylene or the like, Y represents a carbonyl group or the like, A represents -NR^6R^7, R^6 and R^7 may be the same as or different from each other and each represents a hydrogen atom, a lower alkyl group which may have a substituent, or the like, or R^6 and R^7 may be bonded to each other to form a cyclic amino group which may have a substituent. In the formula (H), R^2 is a substituted phenyl group, or the like, and R^3 is any of various substituents. For the other symbols, refer to the respective patent publications.)

[0006] Furthermore, as a guanidino compound having an effect of inhibiting the production and release of inflammatory cytokines, Compound (J) (Patent Document 9) has been reported. However, there is no disclosure or suggestion of a specific compound as the compound of the formula (I) or a salt thereof of the present application as described later in these documents.

[Chem. 3]

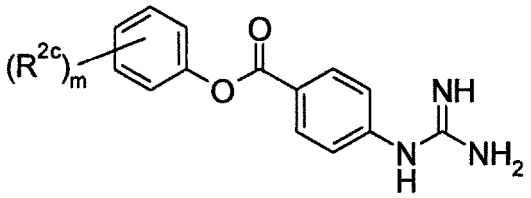


(J)

(wherein R is a guanidino group, an amidino group, or the like; A^1, A^2 and A^3 are each a bond or the like; L is an arylene group or the like; X is -COO- or the like; M is an arylene group or the like, or a divalent heterocyclic group, which has at least one hetero atom selected from a nitrogen atom, a sulfur atom, or an oxygen atom, and may form a fused ring, or the like; R^5 is a hydrogen atom or the like; R^6 is $-CR^{12}R^{13}-(CH_2)_m-R^{11}$ or the like; R^{12} and R^{13} are a hydrogen atom or the like; R^{11} is $-COOR^{16}$ or the like; and R^{16} is a hydrogen atom or the like. For the other symbols, refer to the corresponding patent publications.)

[0007] Furthermore, Compound (K) has been reported as a guanidino compound which is useful as a pollen protease inhibitor (Patent Document 10). However, there is no disclosure or suggestion of a specific compound as the compound of Formula (I) or a salt thereof of the present application as described later in this document.

[Chem. 4]

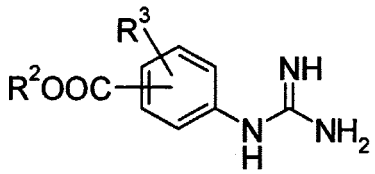


(K)

(wherein R^{2c} represents a $Z^cCONR^{5c}R^{6c}$ group or the like, Z^c represents a bond or the like, R^{5c} and R^{6c} each independently represent a hydrogen atom, an alkyl group having 1 to 4 carbon atoms, an alkyl group having 1 to 4 carbon atoms, substituted with a $COOR^{4c}$ group, a phenyl group, a benzyl group, a pyridyl group, or the like, and R^{4c} represents an alkyl group having 1 to 4 carbon atoms, a phenyl group, or the like).

[0008] Furthermore, a guanidinobenzoic acid derivative (L) which is useful as a house dust mite protease inhibitor has been reported (Patent Document 11). However, there is no disclosure or suggestion of a specific compound as the compound of Formula (I) or a salt thereof of the present application as described later in this document.

[Chem. 5]



(L)

(wherein R^2 represents a phenyl group, a naphthyl group, a substituted phenyl group, or a substituted naphthyl group, and R^3 represents one of various substituents).

Related Art

Patent Document

[0009]

Patent Document 1: JP-A-52-089640
Patent Document 2: JP-A-57-053454
Patent Document 3: WO 1994/013631
Patent Document 4: JP-A-7-053500
Patent Document 5: WO 1991/018869
Patent Document 6: JP-A-8-048664
Patent Document 7: WO 2011/071048
Patent Document 8: WO 1997/037969
Patent Document 9: JP-A-9-124571
Patent Document 10: JP-A-10-306025
Patent Document 11: JP-A-6-192085

Disclosure of Invention

Problems to Be Solved by the Invention

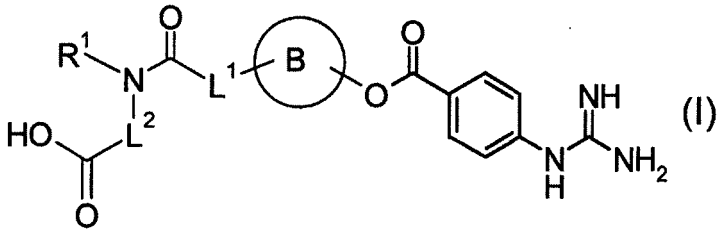
[0010] A guanidinobenzoic acid ester compound, which is useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for preventing and/or treating kidney diseases, is provided.

Means for Solving the Problems

[0011] The ingested proteins from meals are digested by various enzymes in the duodenum and intestine, and finally absorbed as amino acids or peptides. Trypsin which is produced in the pancreas and secreted in the small intestine in the proteolytic process is an important proteolytic enzyme. Further, by suppressing the enzyme it is expected that the low-protein diet state in which the diet-derived proteolysis is suppressed and the absorption is also suppressed may be mimicked. That is, it is considered that a trypsin inhibitor which acts in the gut may potentially be used as an agent that will substitute low-protein diet therapy. In this regard, the present inventors have conducted extensive studies on compounds having a trypsin inhibitory activity. As a result, they have found that the guanidinobenzoic acid ester compound of the present invention has a trypsin inhibitory activity, and is useful for prevention and treatment of kidney diseases as an agent which will substitute the low-protein diet therapy, thereby completing the present invention.

[0012] Specifically, the present invention relates to a compound of the formula (I) or a salt thereof, and a pharmaceutical composition including the compound of the formula (I) or a salt thereof, and an excipient.

[Chem. 6]



(I)

(in which

L^1 is a bond or -lower alkylene-,
L^2 is lower alkylene which may be substituted,
R^1 is lower alkyl which may be substituted with a substituent selected from the group consisting of aryl which may be substituted, an aromatic heterocyclic group which may be substituted, and $-CO_2H$, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form cyclic amino which may be

substituted with-CO_2H, and
Ring B is naphthalenediyl, 1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, benzothiophenediyl, benzofurandiyl, or 2,3-dihydrobenzofurandiyl).

[0013] Furthermore, unless specified otherwise, in the case where the symbols of the formulae in the present specification are also used in other chemical formulae, the same symbols denote the same meanings.

[0014] Moreover, the present invention relates to a pharmaceutical composition for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), and/or a pharmaceutical composition for preventing and/or treating trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like), comprising the compound of Formula (I) or a salt thereof. Further, the pharmaceutical composition includes an agent for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), and/or trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like), comprising the compound of Formula (I) or a salt thereof. In one embodiment, the kidney disease is chronic kidney disease. In one embodiment, the chronic kidney disease is diabetic nephropathy, chronic nephritis, nephrotics, nephrosclerosis, or polycystic kidney disease.

[0015] In addition, the present invention relates to use of the compound of Formula (I) or a salt thereof for the manufacture of a pharmaceutical composition for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), and/or trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like); use of the compound of Formula (I) or a salt thereof for treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), and/or trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like); the compound of Formula (I) or a salt thereof for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), and/or trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like); and a method for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), or trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like), comprising administering an effective amount of the compound of Formula (I) or a salt thereof to a subject. Further, the "subject" is a human or another mammal in need of such prevention or treatment, and in a certain embodiment, a human in need of such prevention or treatment.

Effects of the Invention

[0016] The compound of Formula (I) or a salt thereof has a trypsin inhibitory action, and therefore, can be used as an agent for preventing and/or treating kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), as an agent which will substitute low-protein diet therapy, and/or an agent for preventing and/or treating trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like).

Embodiments for Carrying Out the Invention

[0017] Hereinafter, the present invention will be described in detail.

[0018] In the present specification, the "lower alkyl" refers to linear or branched alkyl having 1 to 6 carbon atoms (which is hereinafter simply referred to as C_{1-6}), examples of which include methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, and the like; in another embodiment, C_{1-3} alkyl; in a further embodiment, methyl, ethyl, propyl, or isopropyl; in a still further embodiment, methyl or ethyl; in a still further embodiment, methyl; and in a still further embodiment, ethyl.

[0019] The "lower alkylene" refers to a divalent group formed by the removal of any one hydrogen atom of the "lower alkyl", examples of which include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, dimethylmethylene, ethylmethylene, isobutylmethylene, methylethylene, dimethylethylene, isobutylene, methylpropylene, ethylethylene, methyltetramethylene, methyltrimethylene, dimethyltetramethylene, and the like; in another embodiment, methylene, methylmethylene, and ethylene; in a further embodiment, C_{1-3} alkylene; in a still further embodiment, methylene, and ehtylene; in a still further embodiment, methylene; and in a still further embodiment, ethylene.

[0020] The "aryl" refers to a monocyclic to tricyclic aromatic hydrocarbon ring group having 6 to 14 carbon atoms, and specifically, phenyl, naphthyl, anthranyl and the like; in a further embodiment, phenyl; and in a still further embodiment, naphthyl.

[0021] The "aromatic heterocyclic group" is an aromatic monocyclic heterocyclic group having 5 to 6 ring members,

containing at least one hetero atom selected from O, N, and S as a ring-constituting atom, or an aromatic bicyclic heterocyclic group formed by fusion of the aromatic monocyclic heterocycle with a benzene ring or a thiophene ring, specific examples of which include pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thienopyridyl, thienopyrimidinyl, thienopyrazinyl, and the like; in one embodiment, an aromatic monocyclic heterocyclic group; in another embodiment, an aromatic bicyclic heterocyclic group; in a further embodiment, thienyl, imidazolyl, thiazolyl, oxadiazolyl, tetrazolyl, indolyl, and benzothienyl; and in a still further embodiment, thienyl and benzothienyl.

[0022] The "non-aromatic heterocyclic group" is a non-aromatic monocyclic heterocyclic group having 3 to 7 ring members, containing at least one hetero atom selected from O, N, and S as a ring-constituting atom, or a non-aromatic bicyclic heterocyclic group formed by fusion of the non-aromatic heterocycle with a benzene ring, a thiophene ring, or a cyclohexane ring, in which a part of the bonds may be unsaturated. Further, the sulfur atom that is a ring-constituting atom may be oxidized. The non-aromatic heterocycle may also be substituted with -oxo. Specific examples thereof include azepanyl, diazepanyl, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl, piperazinyl, azocanyl, thiomorpholinyl, thiazolidinyl, 1,1-dioxidothiazolidinyl, isothiazolidinyl, 1,1-dioxidoisothiazolidinyl, oxazolidinyl, morpholinyl, 1,1-dioxidothiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and the like; in another embodiment, pyrrolidinyl, tetrahydroquinolyl, and tetrahydroisoquinolyl; in a further embodiment, tetrahydroquinolyl and tetrahydroisoquinolyl; and in a still further embodiment, tetrahydroisoquinolyl.

[0023] The "cyclic amino" is a non-aromatic heterocyclic group having a nitrogen atom, which has a bonding arm on the nitrogen atom, among the above "non-aromatic heterocyclic groups". Specific examples of the cyclic amino include azepan-1-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, thiomorpholin-4-yl, thiazolidin-3-yl, 1,1-dioxidothiazolidin-3-yl, isothiazolidin-2-yl, 1,1-dioxidoisothiazolidin-2-yl, oxazolidin-3-yl, morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, and the like; in another embodiment, 1,2,3,4-tetrahydroquinolin-1-yl and 1,2,3,4-tetrahydroisoquinolin-2-yl; and in a further embodiment, 1,2,3,4-tetrahydroisoquinolin-2-yl.

[0024] The "halogen" refers to F, Cl, Br, or I; and in another embodiment, F or Cl.

[0025] In one embodiment of the "naphthalenediyl", naphthalene-1,6-diyl or naphthalene-2,6-diyl is involved; in one embodiment of "1,2,3,4-tetrahydronaphthalenediyl", 1,2,3,4-tetrahydronaphthalene-1,6-diyl or 1,2,3,4-tetrahydronaphthalene-2,6-diyl is involved; in one embodiment of "2,3-dihydroindenediyl", 2,3-dihydroindene-1,5-diyl is involved; in one embodiment of "benzothiophenediyl", benzothiophene-2,6-diyl or benzothiophene-3,6-diyl is involved; in one embodiment of "benzofurandiyl", benzofuran-3,6-diyl is involved; and in one embodiment of "2,3-dihydrobenzofurandiyl", 2,3-dihydrobenzofuran-3,6-diyl is involved.

[0026] The "biological equivalent of $-CO_2H$" means another atom or atom group having common biological properties equivalent to $-CO_2H$, which is capable of releasing acidic protons. Examples thereof include -C(O)-NH-OH, -C(O)-NH-O-lower alkyl, -C(O)-NH-CN, -C(O)-NH-$S(O)_2$-lower alkyl, -C(O)-NH-$S(O)_2$-N(lower alkyl)$_2$, tetrazolyl, oxadiazolonyl, oxadiazolethionyl, oxathiadiazolyl, thiadiazolonyl, triazolethionyl, hydroxyisoxazolyl, and the like; in another embodiment, -C(O)-NH-$S(O)_2$-lower alkyl,-C(O)-NH-$S(O)_2$-N(lower alkyl)$_2$, and tetrazolyl; and in a further embodiment, tetrazolyl.

[0027] In the present specification, the expression "which may be substituted" represents non-substitution or substitution with 1 to 5 substituents". Further, regarding having a plurality of substituents, the substituents may be the same as or different from one another.

[0028] Examples of the substituent in the "lower alkylene which may be substituted" in L^2 of Formula (I) include substituents selected from Group D1.

Group D1:

(1) halogen,
(2) -OH and -O-lower alkyl,
(3) -SH and -S-lower alkyl,
(4) -S(O)-lower alkyl and -$S(O)_2$-lower alkyl,
(5) -CN,
(6) -NO_2,
(7) -NH_2, -NH-(lower alkyl), and -N(lower alkyl)$_2$,
(8) -C(O)-lower alkyl,
(9) aryl substituted with at least one substituent selected from the group consisting of lower alkyl which may be substituted with at least one substituent selected from the group consisting of halogen and $-CO_2H$, -O-(lower alkyl which may be substituted with at least one $-CO_2H$ group), halogen, and $-CO_2H$, and
(10) -C(O)-O-lower alkyl and $-CO_2H$ or a biological equivalent thereof.

[0029] In another embodiment, Group D 1 includes:

(1) aryl substituted with at least one $-CO_2H$ group, and
(2) $-CO_2H$.

[0030] Examples of the substituent in the "aryl which may be substituted" and the "aromatic heterocyclic group which may be substituted" in R^1 of Formula (I) include substituents selected from Group D2.

Group D2:

(1) halogen,
(2) -OH and -O-lower alkyl,
(3) -SH and -S-lower alkyl,
(4) -S(O)-lower alkyl and $-S(O)_2$-lower alkyl,
(5) -CN,
(6) $-NO_2$,
(7) $-NH_2$, -NH-(lower alkyl), and $-N(\text{lower alkyl})_2$,
(8) -C(O)-lower alkyl,
(9) $-C(O)-NH_2$, -C(O)-NH-(lower alkyl), and $-C(O)-N(\text{lower alkyl})_2$,
(10) -C(O)-O-lower alkyl and $-CO_2H$ or a biological equivalent thereof, and
(11) lower alkyl and -O-lower alkyl, each of which may be substituted with at least one substituent selected from the group consisting of the substituents described in (1) to (10) above.

[0031] In another embodiment, Group D2 includes:

(1) $-CO_2H$, and
(2) lower alkyl substituted with at least one $-CO_2H$ group.

[0032] One embodiment of the compound of Formula (I) or a salt thereof is shown below.

(1) The compound or a salt thereof, in which L^1 is a bond or methylene; in another embodiment, the compound or a salt thereof, in which L^1 is a bond; in a further embodiment, the compound or a salt thereof, in which L^1 is lower alkylene; in a still further embodiment, the compound or a salt thereof, in which L^1 is methylene; and in a still further embodiment, the compound or a salt thereof, in which L^1 is a bond or C_{1-3} alkylene.
(2) The compound or a salt thereof, in which L^2 is lower alkylene which may be substituted with a substituent selected from Group D1; in another embodiment, the compound or a salt thereof, in which L^2 is lower alkylene which may be substituted with at least one substituent selected from the group consisting of aryl substituted with at least one $-CO_2H$ group, and $-CO_2H$; in a further embodiment, the compound or a salt thereof, in which L^2 is lower alkylene; in a still further embodiment, the compound or a salt thereof, in which L^2 is C_{1-3} alkylene; in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene, ethylene, or ethylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene; in a still further embodiment, the compound or a salt thereof, in which L^2 is ethylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene, methylmethylene, ethylene, 2-(carboxymethyl)trimethylene, or methylmethylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene, methylmethylene, ethylene, or methylmethylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene, methylmethylene, or methylmethylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is C_{1-3} alkylene substituted with (phenyl substituted with $-CO_2H$); in a still further embodiment, the compound or a salt thereof, in which L^2 is methylene or methylmethylene; in a still further embodiment, the compound or a salt thereof, in which L^2 is methylmethylene substituted with (phenyl substituted with $-CO_2H$).
(3) The compound or a salt thereof, in which R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) $-CO_2H$, or H; in another embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group substituted with a substituent selected from Group D2, and iii) $-CO_2H$, or H; in a further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which may

be substituted with at least one substituent selected from the group consisting of i) aryl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) an aromatic heterocyclic group substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and iii) -CO_2H, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and iii) -CO_2H, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and iii) -CO_2H, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is (phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H)-CH_2-, (thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H)-CH_2-, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is (phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H)-CH_2-; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl substituted with thienyl substituted with at least one -CO_2H group; in a still further embodiment, the compound or a salt thereof, in which R^1 is (thienyl substituted with at least one -CO_2H group)-CH_2-; in a still further embodiment, the compound or a salt thereof, in which R^1 is (phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H)-CH_2-, (thienyl substituted with at least one -CO_2H group)-CH_2-, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is H; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) -CO_2H, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with at least one -CO_2H group; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which is substituted with at least one substituent selected from the group consisting of i) phenyl which may be substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) an aromatic heterocyclic group selected from thienyl and benzothienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and may be substituted with at least one -CO_2H group, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with two -CO_2H groups; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, iii) benzothienyl substituted with -CO_2H, and iv) -CO_2H, or H; in a still further embodiment, the compound or a salt thereof, in which R^1 is (phenyl substituted with -CO_2H)-CH_2-, (phenyl substituted with -CH_2-CO_2H)-CH_2-, or (thienyl substituted with -CO_2H)-CH_2-; in a still further embodiment, the compound or a salt thereof, in which R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with two -CO_2H groups; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl which is substituted with at least one substituent selected from the group consisting of i) phenyl which may be substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) an aromatic heterocyclic group selected from thienyl and benzothienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and may be substituted with at least one -CO_2H group; in a still further embodiment, the compound or a salt thereof, in which R^1 is lower alkyl substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H.

(4) The compound or a salt thereof, in which Ring B is naphthalenediyl, 1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, or benzothiophenediyl; in another embodiment, the compound or a salt thereof, in which Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, or benzothiophene-3,6-diyl; in a further embodiment, the compound or a salt thereof, in which Ring B is naphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, or 1,2,3,4-tetrahydronaphthalene-2,6-diyl; in a still further embodiment, the compound or a salt thereof, in which Ring B is naphthalene-

1,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl in which the position 1 of 1,2,3,4-tetrahydronaphthalenediyl is bonded with L^1, or 1,2,3,4-tetrahydronaphthalene-2,6-diyl in which the position 2 of 1,2,3,4-tetrahydronaphthalenediyl is bonded with L^1; in a still further embodiment, the compound or a salt thereof, in which Ring B is 1,2,3,4-tetrahydronaphthalene-1,6-diyl having the position 1 bonded with L^1, or 1,2,3,4-tetrahydronaphthalene-2,6-diyl having the position 2 bonded with L^1; in a still further embodiment, the compound or a salt thereof, in which Ring B is 1,2,3,4-tetrahydronaphthalene-1,6-diyl having the position 1 bonded with L^1; in a still further embodiment, the compound or a salt thereof, in which Ring B is 1,2,3,4-tetrahydronaphthalene-2,6-diyl having the position 2 bonded with L^1; in a still further embodiment, the compound or a salt thereof, in which Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, benzothiophene-3,6-diyl, benzofuran-3,6-diyl, or 2,3-dihydrobenzofuran-3,6-diyl.

(5) The compound or a salt thereof, in which -L^1-Ring B- is -lower alkylene-(1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, benzofurandiyl, or 2,3-dihydrobenzofurandiyl); in another embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, benzofurandiyl, or 2,3-dihydrobenzofurandiyl); in a further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalenediyl) or -CH_2-(2,3-dihydroindenediyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalenediyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is CH_2-(2,3-dihydroindenediyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalene-1,6-diyl) or -CH_2-(1,2,3,4-tetrahydronaphthalene-2,6-diyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalene-1,6-diyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalene-2,6-diyl); in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalene-1,6-diyl) in which CH_2 is bonded with the position 1 of 1,2,3,4-tetrahydronaphthalenediyl; in a still further embodiment, the compound or a salt thereof, in which -L^1-Ring B- is -CH_2-(1,2,3,4-tetrahydronaphthalene-2,6-diyl) in which CH_2 is bonded with the position 2 of 1,2,3,4-tetrahydronaphthalenediyl.

(6) The compound or a salt thereof, which is a combination of any two or more of the embodiments as described in (1) to (5) above.

The compound or a salt thereof, which is a combination of any two or more of the embodiments of (1) to (5) above, as described in (6) above, is also included in the present invention, and the specific examples thereof also include the following embodiments.

(7) The compound or a salt thereof, in which L^1 is a bond or methylene, L^2 is lower alkylene which may be substituted with a substituent selected from Group D1, R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) -CO_2H, or H, and Ring B is naphthalenediyl, 1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, or benzothiophenediyl.

(8) The compound or a salt thereof as described in (7), in which L^2 is methylene, ethylene, or ethylene substituted with (phenyl substituted with -CO_2H).

(9) The compound or a salt thereof as described in (7), in which L^2 is methylene, methylmethylene, ethylene, or methylmethylene substituted with (phenyl substituted with -CO_2H).

(10) The compound or a salt thereof as described in (8) or (9), in which R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and iii) -CO_2H, or H.

(11) The compound or a salt thereof as described in (10), in which Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, or benzothiophene-3,6-diyl.

(12) The compound or a salt thereof as described in (11), in which L^2 is methylene or methylmethylene, and R^1 is lower alkyl substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, or L^2 is methylmethylene substituted with (phenyl substituted with -CO_2H), and R^1 is H.

(13) The compound or a salt thereof as described in (12), in which L^2 is methylene or methylmethylene, and R^1 is (phenyl substituted with -CO_2H)-CH_2-, (phenyl substituted with -CH_2-CO_2H)-CH_2-, or (thienyl substituted with -CO_2H)-CH_2-.

(14) The compound or a salt thereof as described in (12), in which L^2 is methylmethylene substituted with (phenyl substituted with -CO_2H), and R^1 is H.

(15) The compound or a salt thereof, in which L^1 is a bond or C_{1-3} alkylene, L^2 is lower alkylene which may be substituted with a substituent selected from Group D1, R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) $-CO_2H$, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with at least one $-CO_2H$ group.
(16) The compound or a salt thereof as described in (15), in which L^1 is a bond or methylene, Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, benzothiophene-3,6-diyl, benzofuran-3,6-diyl, or 2,3-dihydrobenzofuran-3,6-diyl, and

a) L^2 is C_{1-3} alkylene, and R^1 is lower alkyl which is substituted with at least one substituent selected from the group consisting of i) phenyl which may be substituted with at least one substituent selected from the group consisting of $-CO_2H$ and lower alkyl substituted with $-CO_2H$, and ii) an aromatic heterocyclic group selected from thienyl and benzothienyl substituted with at least one substituent selected from the group consisting of $-CO_2H$ and lower alkyl substituted with $-CO_2H$, and may be substituted with at least one $-CO_2H$ group,
b) L^2 is C_{1-3} alkylene substituted with (phenyl substituted with $-CO_2H$), and R^1 is H, or
c) R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with two $-CO_2H$ groups.

[0033] Examples of the specific compounds included in the compound of Formula (I) or a salt thereof include the following compounds:

4-{[{6-[(4-carbamimidamidobenzoyl)oxy]-2-naphthoyl}(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
3-{[({(1S)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
N-{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}-4-carboxy-L-phenylalanine,
4-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}carbonyl)(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[({5-[(4-carbamimidamidobenzoyl)oxy]-2,3-dihydro-1H-inden-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
4-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1-benzothiophen-3-yl}carbonyl)(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}(carboxymethyl)amino]methyl}benzoic acid,
N-{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}-N-[4-(carboxymethyl)benzyl]glycine,
4-({({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)[(1R)-1-carboxyethyl]amino}methyl)thiophene-2-carboxylic acid,
4-({({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}carbonyl)[(1R)-1-carboxyethyl]amino}methyl)thiophene-2-carboxylic acid, or
N-({6-[(4-carbamimidamidobenzoyl)oxy]-1-benzothiophen-3-yl}carbonyl)-N-[4-(carboxymethyl)benzyl]glycine,

or a salt thereof.

[0034] The compound of the formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of the formula (I) shall be described in only one form of isomer, yet the present invention includes other isomers, isolated forms of the isomers, or a mixture thereof.

[0035] In addition, the compound of the formula (I) may have asymmetric carbon atoms or axial asymmetry in some cases, and correspondingly, it may exist in the form of optical isomers based thereon. The present invention includes both an isolated form of the optical isomers of the compound of the formula (I) or a mixture thereof.

[0036] Moreover, the present invention also includes a pharmaceutically acceptable prodrug of the compound represented by the formula (I). The pharmaceutically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in Prog. Med., 5, 2157-2161 (1985) and "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990), Vol. 7, Molecular Design, 163-198.

[0037] Furthermore, the salt of the compound of the formula (I) is a pharmaceutically acceptable salt of the compound of the formula (I) and may form an acid addition salt or a salt with a base depending on the kind of substituents. Specific

examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid, and the like, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, aluminum, and the like or organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine, and the like, salts with various amino acids or amino acid derivatives such as acetylleucine and the like, ammonium salts, etc.

[0038] In addition, the present invention also includes various hydrates or solvates, and polymorphic crystalline substances of the compound of the formula (I) and salts thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

(Preparation Methods)

[0039] The compound of the formula (I) and a salt thereof can be prepared using the characteristics based on the basic structure or the type of substituents thereof and by applying various known synthesis methods. During the preparation, replacement of the relevant functional group with a suitable protective group (a group that can be easily converted into the relevant functional group) at the stage from starting material to an intermediate may be effective depending on the type of the functional group in the production technology in some cases. The protective group for such a functional group may include, for example, the protective groups described in "Greene's Protective Groups in Organic Synthesis (4th edition, 2006)", P. G. M. Wuts and T. W. Greene, and one of these may be selected and used as necessary depending on the reaction conditions. In this kind of method, a desired compound can be obtained by introducing the protective group, by carrying out the reaction and by eliminating the protective group as necessary.

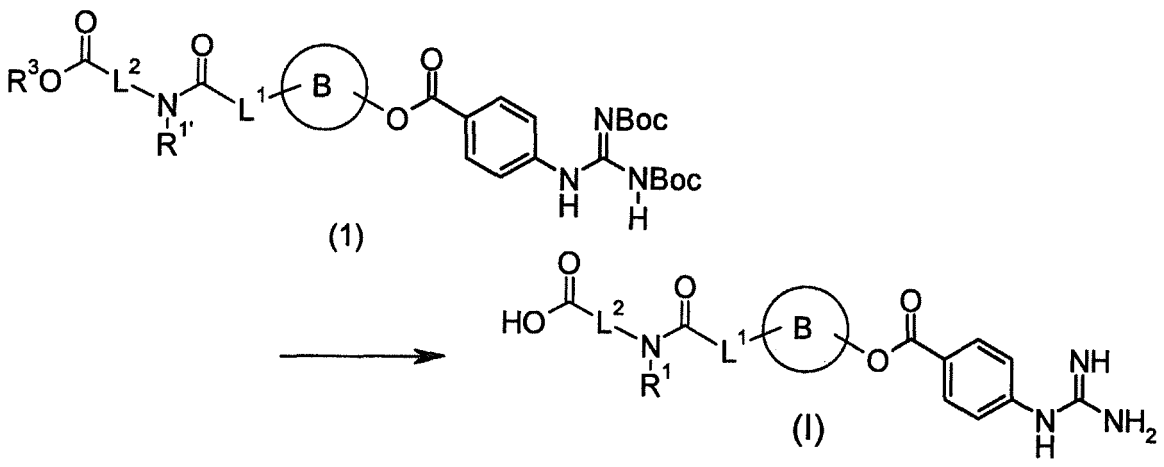
[0040] In addition, the prodrug of the compound of the formula (I) can be prepared by introducing a specific group at the stage from a starting material to an intermediate, or by carrying out the reaction using the obtained compound of the formula (I), as in the case of the above-mentioned protective group. The reaction can be carried out using methods known to those skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

[0041] Hereinbelow, the representative preparation methods for the compound of the formula (I) will be described. Each of the production processes may also be carried out with reference to the references appended in the present description. Further, the preparation methods of the present invention are not limited to the examples as shown below.

(Production Process 1)

[0042]

[Chem. 7]



(in which R^3 represents H or tert-butyl, Boc represents tert-butoxycarbonyl, and R^1 represents a group described in R^1 and a group having $-CO_2$-tert-butyl as a substituent).

[0043] The present production process is a method for preparing a compound (I) which is the compound of the present

invention by deprotecting Compound 1.

[0044] The present step is carried out by using Compound 1 and a deprotecting reagent in equivalent amounts, or either thereof in an excess amount, and stirring the mixture in a solvent which is inert to the reaction or in the absence of a solvent, in a range of from cooling to heating and refluxing, usually for 0.1 hours to 5 days. Examples of the solvent used herein are not particularly limited, but include ethers such as diethylether, tetrahydrofuran (THF), 1,4-dioxane, and dimethoxyethane, and halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like. Examples of the deprotecting reagent are not particularly limited, but include a solution of hydrogen chloride in 1,4-dioxane, a solution of hydrogen chloride in ethyl acetate, trifluoroacetic acid, and the like.

[0045] In addition, in the case where a -CO_2-tert-butyl group is present as a substituent in $R^{1'}$, the tert-butyl group is deprotected at the same time in the present step.

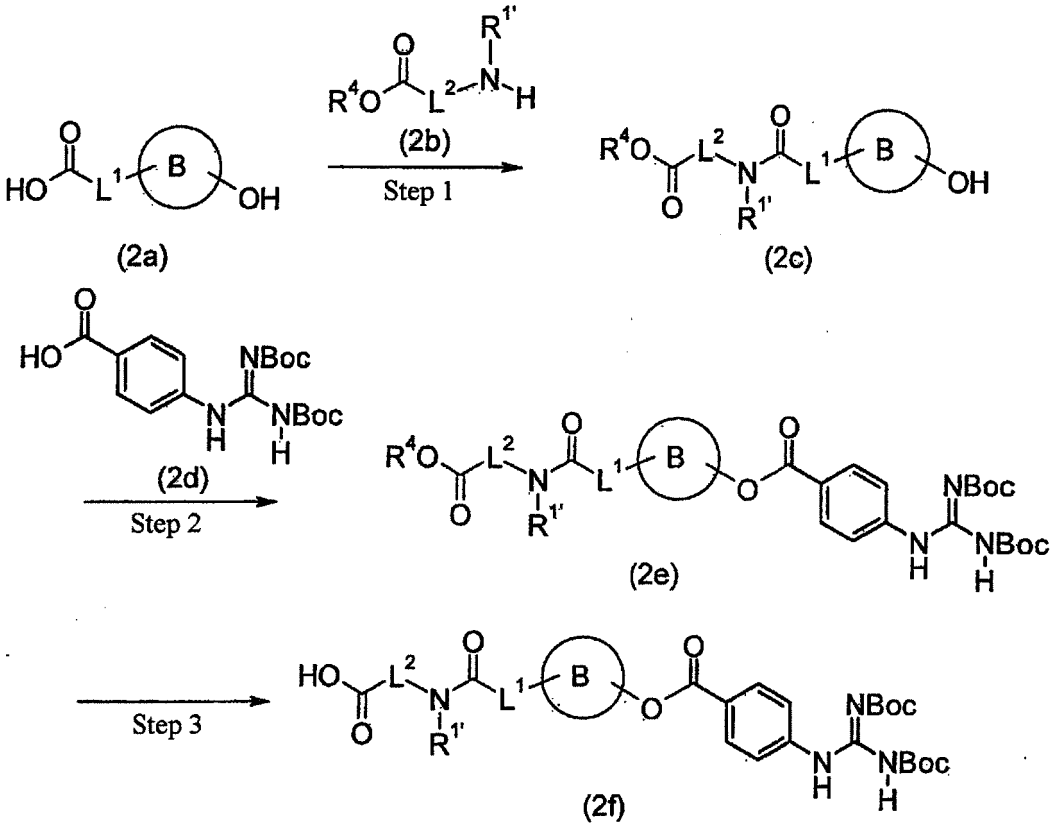
(Preparation of Starting Compound)

[0046] The starting compound in the preparation method above can be prepared by using, for example, the method below, the method described in Preparation Examples as described later, a known method, or a modified method thereof.

(Starting Material Synthesis 1)

[0047]

[Chem. 8]



(in which R^4 represents a tert-butyl group or a benzyl group).

[0048] The present production process is a method for preparing Compound 2e or 2f which is Starting Compound 1 of the production process 1.

(Step 1)

[0049] The present step is a step of obtaining Compound 2c by subjecting Compound 2a and Compound 2b to amidation.

[0050] The present step is carried out by using Compound 2a and Compound 2b in equivalent amounts, or either thereof in an excess amount, and stirring the mixture in a solvent which is inert to the reaction, in a range of from cooling to heating and refluxing, and preferably from -20°C to 60°C, usually for 0.1 hours to 5 days, in the presence of a condensing agent. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, and xylene, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, and dimethoxyethane, N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate, acetonitrile, water, and a mixture thereof. Examples of the condensing agent include, but are not limited to, N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride, dicyclohexylcarbodiimide, 1,1'-carbonylbis-1H-imidazole, diphenylphosphoryl azide, phosphorus oxychloride, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU), and the like. It is preferable in some cases for the progress of the reaction to use an additive such as 1H-benzotriazol-1-ol. In addition, it is preferable in some cases for the smooth progress of the reaction to use organic bases such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, and pyridine, or inorganic bases such as potassium carbonate, sodium carbonate, and potassium hydroxide.

[0051] Further, Compounds 2a and 2b are commercially available, and can be prepared by a known method (for example, Journal of Medicinal Chemistry, 2003, Vol. 46, No. 12, pp. 2446-2455; WO2006/083781; or the like) or a method equivalent thereto, or the method described in Preparation Examples as described later.

(Step 2)

[0052] The present step is a step of obtaining Compound 2e by subjecting Compound 2c and Compound 2d to esterification.

[0053] In the present step, a method equivalent to Step 1 of Starting Material Synthesis 1 can be used.

[0054] Further, Compound 2d can be prepared by a known method (for example, Tetrahedron Letters, 1993, Vol. 34, No. 21, pp. 3389-3392) or a method equivalent thereto.

(Step 3)

[0055] The present step is a step of obtaining Compound 2f having a benzyl group deprotected, in the case where R^4 in Compound 2e is the benzyl group.

[0056] In the present step, Compound 2e is stirred in a solvent which is inert to the reaction, in a hydrogen atmosphere, in the presence of a metal catalyst, usually for 1 hour to 5 days. This reaction is usually carried out in a range of from cooling to heating, and preferably at room temperature. Examples of the solvent used herein are not particularly limited, but include alcohols such as methanol, ethanol, and 2-propanol, ethers such as diethylether, tetrahydrofuran, 1,4-dioxane, and dimethoxyethane, water, ethyl acetate, N,N-dimethylformamide, dimethyl sulfoxide, and a mixture thereof. As the metal catalyst, palladium catalysts such as palladium carbon, palladium black, and palladium hydroxide, platinum catalysts such as platinum oxide, nickel catalysts such as reduced nickel and Raney nickel, or rhodium catalysts such as tris(triphenylphosphine)chlororhodium are suitably used. It is also possible to use formic acid or ammonium formate as a hydrogen source in an equivalent amount or an excess amount with respect to that of the compound 2e.

[Documents]

[0057]

M. Hudlicky, "Reductions in Organic Chemistry, 2nd edition (ACS Monograph: 188)", ACS, 1996

"Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", edited by The Chemical Society of Japan, Vol. 19 (2005) (Maruzen)

[0058] The compounds of the formula (I) can be isolated and purified as their free compounds, salts, hydrates, solvates, or polymorphic crystalline substances thereof. The salts of the compound of the formula (I) can be prepared by carrying out the treatment of a conventional salt forming reaction.

[0059] Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, various types of fractional chromatography, and the like.

[0060] Various isomers can be prepared by selecting an appropriate starting compound or separated by using the difference in the physicochemical properties between the isomers. For example, the optical isomers can be obtained by means of a general method for designing optical resolution of racemic products (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, chromatography using a chiral column or the like, and others), and further, the isomers can also be prepared from an appropriate optically active starting compound.

[0061] The pharmacological activity of the compound of the formula (I) was confirmed by the tests shown below.

1. Confirmation of Trypsin Inhibitory Activity in Humans and Mice

[0062] In the experiment, human recombinant trypsin (rh-trypsin; manufactured by Wako Pure Chemical Industries, Ltd.), cat. #206-17171) and mouse trypsin (m-trypsin; purified from the mouse small intestine contents by the present inventors) were used. The method for purifying m-trypsin from the contents of the mouse small intestine is shown below.

[0063] The small intestine contents and the gastrointestinal tract obtained from 10 mice were homogenized in phosphate buffer saline (PBS) using Polytron, and subjected to centrifugation several times at 15,000 × g for 10 minutes. The supernatant was mixed at 4°C for 16 hours with a Benzamidine Sepharose 4 Fast Flow Resin (GE Healthcare: #17-5123-10). After washing the resin with PBS, m-trypsin was eluted with a glycine buffer (pH 3.0) to carry out purification. It was confirmed by Western blot analysis that the obtained purified fraction was recognized as an Anti-mouse Trypsin Antibody (Santa Cruz Biotechnology, Inc.: sc-67388). The method for measuring the trypsin inhibiting activity is shown below.

[0064] The compound was dissolved in dimethyl sulfoxide (DMSO), and diluted to an arbitrary concentration (A). A was 100-fold diluted with a buffer (0.1 M Tris (pH 8.0), 0.15 M NaCl, 10 mM $CaCl_2$, 0.05% Brij35) (B). The rh-trypsin was diluted with a buffer to 0.088 μg/mL, and for the m-trypsin, the purified fraction liquid was 50-fold diluted with the buffer (C). The dilution ratio of the m-trypsin was set to exhibit the same activity as the 0.088 μg/mL of rh-trypsin as determined by kinetic analysis. A BZiPAR solution (Rhodamine Reference Substrate) which is substrate for the trypsin enzyme was diluted with the buffer to 5 μmol/L (D). 5 μL of B, 5 μL of C, and 10 μL of D were added to a 384-well plate, and incubated at room temperature for 30 minutes. Fluorescent signals were detected at a maximum excitement (Ex)/fluorescent wavelength (Em) = 497 nm/520 nm using a Tecan Safire Fluorometer. The compound was studied at 2500 nM, 750 nM, 250 nM, 75 nM, 25 nM, 7.5 nM, 2.5 nM, 0.75 nM, 0.25 nM, 0.075 nM, 0.025 nM, and 0.0075 nM, and the inhibitory rate of each compound was calculated by assuming the inhibition without addition of the compound (DMSO alone) in the presence of an enzyme as 0% inhibition, and assuming the inhibition without addition of the compound in the absence of an enzyme as 100% inhibition. Based on the obtained inhibitory rates, the trypsin inhibitory activities (IC_{50} values, nM) were calculated from the non-linear regression.

[0065] The results of the test are shown in Table 1. Ex in the tables represents the Example No. as denoted below (which shall apply hereinafter).

[Table 1]

Ex	r-h Trypsin	Mouse trypsin	Ex	r-h Trypsin	Mouse trypsin	Ex	r-h Trypsin	Mouse trypsin
1	0.31	0.41	22	0.34	0.44	42	0.20	0.14
2	0.4	0.51	23	0.46	0.46	43	0.17	0.19
3	0.21	0.22	24	0.23	0.24	44	0.20	0.20
4	0.43	0.61	25	0.28	0.35	45	0.36	0.54
5	0.19	0.27	26	0.33	0.34	46	0.25	0.23
6	0.29	0.20	27	0.32	0.35	47	0.26	0.29
7	0.30	0.26	28	0.38	0.40	48	0.36	0.44
8	0.43	0.57	29	0.26	0.23	49	0.37	0.45
10	1.2	1.4	30	0.25	0.28	50	0.28	0.43
11	0.31	0.68	31	0.23	0.22	51	0.34	0.38
12	1.5	1.7	32	0.15	0.14	52	0.43	0.55
13	0.25	0.36	33	0.18	0.16	53	0.54	0.60
14	0.23	0.26	34	0.21	0.17	54	0.29	0.46
15	0.10	0.18	35	0.37	0.42	55	0.35	0.47

(continued)

Ex	r-h Trypsin	Mouse trypsin	Ex	r-h Trypsin	Mouse trypsin	Ex	r-h Trypsin	Mouse trypsin
16	0.14	0.24	36	0.26	0.28	56	0.35	0.59
17	0.22	0.27	37	0.24	0.18	57	0.19	0.38
18	0.29	0.48	38	0.26	0.23	58	0.68	0.74
19	0.39	0.60	39	0.18	0.13	59	0.71	0.87
20	0.47	0.77	40	0.29	0.27	60	0.33	0.31
21	0.38	0.52	41	0.26	0.22			

[0066] The compound of the present invention exhibited a good trypsin inhibitory activity.

2. Test of Increase in Fecal Protein Concentration Using Mice

[0067] For the experiment, 6-week old male ICR mice were used. The experiment was carried out in five mice per group. After fasting the mice for 15 hours, the control group was forcibly orally administered with a 0.5% methyl cellulose (MC) solution, and the test drug group was forcibly orally administered (5 mg/kg) with a solution or suspension obtained by dissolving or suspending the compound in the 0.5% MC solution. The fasting was stopped immediately thereafter, free feeding (CE-2) was started, and then the feces were collected from after 3 hours to after 9 hours, and weighed. All of the obtained feces were suspended in 6 mL of distilled water, and centrifuged at 1,940 × g for 10 minutes. The protein concentration in the obtained supernatant was measured by a Bradford method, and the amount of the protein in 1 g of feces was calculated by dividing the protein concentration in the feces by the total weight of feces. Further, the efficacy was investigated from the ratio to the control group. For the compounds that were evaluated multiple times, the average values were calculated.

[0068] The results of the activities with an increase in Fecal Protein, assuming a value for the control group as 1, are shown in Table 2.

[Table 2]

Ex	Folds (vs. control)	Ex	Folds (vs. control)	Ex	Folds (vs. control)
1	2.00	30	1.68	56	1.45
2	2.55	31	1.51	57	2.25
3	2.09	32	1.90	58	2.18
4	2.62	33	1.39	59	1.64
5	1.88	34	2.07	60	2.26
6	1.84	35	1.59		
7	1.83	36	1.90		
8	1.90	37	1.74		
11	2.63	38	1.91		
13	2.73	39	1.08		
14	1.79	40	1.89		
15	2.61	41	2.01		
16	2.39	42	2.04		
17	2.7	43	1.98		
18	2.18	44	1.72		
19	2.51	45	1.38		
20	2.23	46	1.84		

(continued)

Ex	Folds (vs. control)	Ex	Folds (vs. control)	Ex	Folds (vs. control)
21	2.51	47	1.91		
22	2.15	48	1.79		
23	2.53	49	2.07		
24	1.51	50	1.56		
25	1.35	51	1.66		
26	1.70	52	1.78		
27	1.98	53	1.64		
28	1.54	54	1.70		
29	1.43	55	2.30		

[0069] The compounds shown in the table above exhibited an increased amount of protein in the diet to be discharged as undigested by the trypsin activity inhibitory action, and thus, an inhibited protein uptake in the biological body.

3. Test of Rat Uninephrectomy Doxorubicin (DXR)-Induced Nephropathy Model (Renal Function Reduced Model)

[0070] Uninephrectomy was performed in the left kidney of 10-week old male Wistar rats, and one week later, DXR (5 mg/kg) was administered to the rats via the caudal vein to induce a nephropathy model. The experiment was carried out in ten rats per group. During the period of administering the compound, the rats were fed with diet only in daytime, while fasted in nighttime. A test compound (10 mg/kg) was suspended in a 0.5% methylcellulose (MC) solution from the day after the preparation of the model, and was forcibly orally administered twice (morning and night) daily. To each of a sham (normal) group and a control group, 0.5% MC was forcibly orally administered. At 1, 2, and 3 weeks after the start of administration of the test compound, 24-hour urine collection was each performed to measure the amount of the protein excretion in urine. Blood collection was performed after the end of the urine collection at week 3, and the concentration of creatinine in plasma was measured.

[0071] As a result of the test above, for example, the compound of Example 2 significantly lowered the amount of protein excretion in urine, as compared with the control group, and the inhibitory rate at week 3 was about 42%. Further, the present compound significantly lowered the creatinine concentration in plasma and the inhibitory rate at week 3 was about 42%.

[0072] From the results of the present test, it was confirmed that the compounds exhibited the lowering effects of the protein excretion in urine and the creatinine concentration in plasma, and thus, the progression of the nephropathy was inhibited.

[0073] From the test above, a good inhibitory activity of trypsin and an inhibitory effects for protein absorption based on the inhibition of proteolytic enzymes were confirmed. Further, it was confirmed that, for example, the compound of Example 2 had lowering effect of the amount of protein excretion and the creatinine concentration in plasma in a model with nephropathy showing reduced renal function. Therefore, the compound of Formula (I) can be used as an agent for preventing and/or treating trypsin-related diseases (for example, chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, influenza, and the like), and kidney diseases (for example, chronic kidney disease, acute glomerulonephritis, acute kidney injury, and the like), which will act as an agent which will substitute low protein diet.

[0074] A pharmaceutical composition containing one or two or more kinds of the compound of the formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are usually used in the art, that is, excipients for pharmaceutical preparations, carriers for pharmaceutical preparations, and the like according to the methods usually used.

[0075] Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration, such as injections such as intraarticular, intravenous, and intramuscular injections, suppositories, ophthalmic solutions, eye ointments, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

[0076] The solid composition for use in the oral administration is used in the form of tablets, powders, granules, or the like. In such a solid composition, one or more active ingredient(s) are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives, such as a lubricant, a disintegrating agent, a stabilizer, or a solubilization assisting agent. If necessary, tablets or pills may be coated with sugar or a film of a gastric

or enteric coating substance.

[0077] The liquid composition for oral administration contains pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also contains generally used inert diluents, for example, purified water or ethanol. In addition to the inert diluent, the liquid composition may also contain auxiliary agents, such as a solubilization assisting agent, a moistening agent, and a suspending agent, sweeteners, flavors, aromatics, or antiseptics.

[0078] The injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. Examples of the non-aqueous solvent include alcohols such as ethanol. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizer, or a solubilizing assisting agent. These are sterilized, for example, by filtration through a bacteria retaining filter, by a bactericide being blended in, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending in sterile water or a sterile solvent for injection prior to its use.

[0079] The agent for external use includes ointments, plasters, creams, jellies, poultices, sprays, lotions, eye drops, eye ointments, and the like. The agents contain generally used ointment bases, lotion bases, aqueous or non-aqueous liquid preparations, suspensions, emulsions, and the like.

[0080] As the transmucosal agents such as an inhaler, a transnasal agent, and the like, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a conventionally known method. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizer, a thickening agent, or the like may be appropriately added thereto. For their administration, an appropriate device for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a known device or sprayer, such as a measured administration inhalation device, and the like. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray which uses an appropriate ejection agent, for example, a suitable gas such as chlorofluoroalkane, carbon dioxide, and the like.

[0081] In oral administration, the daily dose is appropriately from about 0.001 to 100 mg/kg, preferably from 0.1 to 30 mg/kg, and more preferably 0.1 to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 separate portions. In the case of intravenous administration, the daily dose is suitably administered from about 0.0001 to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 to 100 mg/kg per body weight, once a day or two or more times a day. The dose is appropriately decided in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

[0082] Although varying depending on administration routes, dosage forms, administration sites, or the types of excipients and additives, the pharmaceutical composition of the present invention contains 0.01 to 100% by weight, and in a certain embodiment, 0.01 to 50% by weight of one or more kinds of the compound of the formula (I) or a salt thereof, which is an active ingredient.

[0083] The compound of the formula (I) or a salt thereof can be used in combination with various agents for treating or preventing the diseases for which the compound of the formula (I) or a salt thereof is considered to be effective, as described above. The combined preparation may be administered simultaneously, or separately and continuously, or at a desired time interval. The preparations to be administered simultaneously may be a blend, or may be prepared individually.

Examples

[0084] Hereinbelow, the preparation methods for the compound of the formula (I) or a salt thereof will be described in more detail with reference to Examples, but the present invention is not limited to the compounds described in the Examples as described below. Furthermore, the production processes for the starting compounds will be described in Preparation Examples. Further, the preparation methods for the compound of the formula (I) are not limited to the preparation methods of the specific Examples as below, but the compound of the formula (I) can be prepared by any combination of the preparation methods or the methods that are apparent to a person skilled in the art.

[0085] Furthermore, the following abbreviations may be used in some cases in the Examples, Preparation Examples, and Tables below.

[0086] PEx: Preparation Example No. (the compounds in which "*" is marked in the chemical and structural formulae denote that the compounds are single isomers having steric configurations of the denoted structures; the compounds in which "**" is marked in the chemical and structural formulae denote that the compounds are single isomers, but have no steric configuration determined; and the compounds in which "#" is marked in the chemical and structural formulae denote a diastereomeric mixture), Ex: Example No. (the compounds in which "*" is marked in the chemical and structural formulae denote that the compounds are single isomers having steric configurations of the denoted structures; the compounds in which "**" is marked in the chemical and structural formulae denote that the compounds are single isomers,

but have no steric configuration determined; and the compounds in which "#" is marked in the chemical and structural formulae denote a diastereomeric mixture), PSyn: Preparation Example No. prepared by the same method, Syn: Example No. prepared by the same method, Str: Chemical Structural formula (Me: methyl, ^{t}Bu: tert-butyl, Ph: phenyl, Boc: tert-butoxycarbonyl, Bn: benzyl, OMe: -O-methyl, OBn: -O-benzyl, O^{t}Bu: -O-tert-butyl, and NBoc: -N-tert-butoxycarbonyl), Data: Physicochemical Data, ESI+: m/z values in mass spectroscopy (Ionization ESI, representing $(M+H)^+$ unless otherwise specified), ESI-: m/z values (Ionization ESI, representing $(M-H)^-$ unless otherwise specified), APCI+: m/z values (atmospheric pressure chemical ionization APCI, representing $(M+H)^+$ unless otherwise specified), APCI/ESI+: APCI/ESI-MS$[M+H]^+$ (APCI/ESI means the simultaneous measurement of APCI and ESI), NMR1: characteristic δ (ppm) in ^{1}H NMR in dimethylsulfoxide-d_6, NMR2: characteristic δ (ppm) in ^{1}H NMR in $CDCl_3$, "M" in Preparation Examples and Examples: mol/L, and RT: a retention time in supercritical chromatography or liquid chromatography, in a unit of minutes (min).

[0087] In addition, in the structural formulae, HCl represents hydrochloride, and TFA represents trifluoroacetate.

Preparation Example 1

[0088] A mixture of tert-butyl 4-methylthiophene-2-carboxylate (12.0 g), N-bromosuccinimide (10.8 g), 2,2'-azobis(isobutyronitrile) (496 mg), and carbon tetrachloride (119 mL) was stirred at 90°C for 1 hour. Further, N-bromosuccinimide (1.08 g) was added thereto, and the mixture was stirred at 90°C for 1 hour. The reaction suspension was cooled to room temperature, then the insoluble material was separated by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-(bromomethyl)thiophene-2-carboxylate (16.3 g).

[0089] To a solution of tert-butyl 4-(bromomethyl)thiophene-2-carboxylate (9.90 g) in N,N-dimethylformamide (100 mL) were added tert-butyl glycinate hydrochloride (18.0 g) and triethylamine (19.9 mL), followed by stirring at 60°C for 15 hours. The reaction suspension was cooled to room temperature, and then sodium triacetoxyborohydride (22.7 g) was added thereto, followed by stirring at room temperature for 5 hours. To the reaction suspension were added water and an aqueous sodium hydrogen carbonate solution, followed by extraction with ethyl acetate. The organic layer was washed with a 5% aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (5.67 g).

Preparation Example 2

[0090] To a solution of 6-hydroxy-2-naphthoic acid (220 mg) in N,N-dimethylformamide (3.30 mL) were added tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (383 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (489 mg), and N,N-diisopropylethylamine (500 μL), followed by stirring at room temperature for 20 hours. Further, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (222 mg) and N,N-diisopropylethylamine (200 μL) were added thereto, followed by stirring at room temperature for 6 hours. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)(6-hydroxy-2-naphthoyl)amino]methyl}thiophene-2-carboxylate (277 mg).

Preparation Example 3

[0091] To a solution of 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (194 mg) in dichloromethane (7.29 mL) were added N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (118 mg), tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)(6-hydroxy-2-naphthoyl)amino]methyl}thiophene-2-carboxylate (255 mg), and 4-dimethylaminopyridine (18.8 mg), followed by stirring at room temperature for 24 hours. To the reaction liquid was added water, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-({[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-2-naphthoyl](2-tert-butoxy-2-oxoethyl)amino}methyl)thiophene-2-carboxylate (137 mg).

Preparation Example 4

[0092] To a solution of 6-methoxy-1-benzothiophene-2-carboxylic acid (960 mg) in dichloromethane (5.76 mL) was added dropwise a 1 M solution (37.5 mL) of boron tribromide in dichloromethane over 10 minutes under ice-cooling,

followed by stirring at room temperature for 3 hours. The reaction liquid was added dropwise to ice, followed by stirring. The precipitate was collected by filtration, and dried under reduced pressure to obtain 6-hydroxy-1-benzothiophene-2-carboxylic acid (920 mg).

Preparation Example 5

[0093] To a solution of 2-tert-butyl 3,7-dimethyl (3R)-3,4-dihydroisoquinoline-2,3,7(1H)-tricarboxylate (345 mg) in methanol (7.00 mL) was added a 1 M aqueous sodium hydroxide solution (3.50 mL), followed by stirring at room temperature for 3 hours. The mixture was neutralized by the addition of 1 M hydrochloric acid (3.50 mL), and then water was added thereto, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain (3R)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid (328 mg).

Preparation Example 6

[0094] To a solution of (6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid (1.03 g) in N,N-dimethylformamide (20.5 mL) were added tert-butyl 3-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate hydrochloride (1.96 g), triethylamine (762 μL), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (1.00 g), and 1H-benzotriazol-1-ol (705 mg), followed by stirring at room temperature for 13 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 3-({(2-tert-butoxy-2-oxoethyl)[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetyl]amino}methyl)benzoate (2.41 g).

Preparation Example 7

[0095] Under a nitrogen atmosphere, to a solution of tert-butyl 3-(chloromethyl)benzoate (29.1 g) in N,N-dimethylformamide (300 mL) were added tert-butyl glycinate hydrochloride (43.0 g) and triethylamine (71.6 mL), followed by stirring at 60°C to 63°C for 3 hours. The reaction mixture was ice-cooled, and then water was added thereto, followed by extraction with ethyl acetate. The organic layer was sequentially washed with a 10% aqueous ammonium chloride solution and a 20% aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL), and then a 4 M solution (32.1 mL) of hydrogen chloride in ethyl acetate was added dropwise thereto under ice-cooling in a nitrogen atmosphere, followed by stirring for 1 hour. The precipitate was collected by filtration, washed with ethyl acetate, and then dried at 50°C under reduced pressure to obtain tert-butyl 3-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate hydrochloride (28.5 g).

Preparation Example 8

[0096] A mixture of ethyl (6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (2.08 g) and 48% hydrobromic acid (40.0 mL) was stirred at 120°C for 17 hours. The reaction mixture was left to be cooled and then concentrated under reduced pressure. To the residue was added tetrahydrofuran (100 mL), followed by stirring at room temperature for 1 hour, and then the precipitate was collected by filtration. The filtrate was concentrated under reduced pressure, and then the residue was purified by silica gel column chromatography (hexane-ethyl acetate). To the purified product was added diisopropylether (15.0 mL), followed by stirring at room temperature for 1 hour. The precipitate was collected by filtration, washed with diisopropylether, and then dried at room temperature under reduced pressure to obtain (6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid (1.06 g).

Preparation Example 9

[0097] To a solution of 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (1.97 g) in dichloromethane (48.0 mL) were added tert-butyl 3-({(2-tert-butoxy-2-oxoethyl)[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetyl]amino}methyl)benzoate (2.40 g), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (1.17 g), and 4-dimethylaminopyridine (173 mg), followed by stirring at room temperature for 2 hours. Further, 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (179 mg) and N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (100 mg) were added thereto, followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 3-{[{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate (3.71 g).

Preparation Example 10

[0098] To a solution of tert-butyl N-[(benzyloxy)carbonyl]-4-(tert-butoxycarbonyl)-L-phenylalaninate (570 mg) in tetrahydrofuran (3.00 mL) and ethanol (3.00 mL) was added 10% palladium-carbon (138 mg, a 50% wet product) in an argon atmosphere, followed by stirring at room temperature overnight at normal pressure in a hydrogen atmosphere. The reaction suspension was filtered by passing it through a Celite (registered trademark) layer, and then the filtrate was concentrated under reduced pressure to obtain tert-butyl 4-(tert-butoxycarbonyl)-L-phenylalaninate (431 mg).

Preparation Example 11

[0099] A mixture of 3-[(benzyl{[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]pentanedioic acid (886 mg), N,N-dimethylformamide di-tert-butyl acetal (1.60 mL), and toluene (4.43 mL) was stirred at 80°C for 4 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain di-tert-butyl 3-[(benzyl{[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]pentanedioate (232 mg).

Preparation Example 12

[0100] To 3,7-dibenzyl 2-tert-butyl (3R)-3,4-dihydroisoquinoline-2,3,7(1H)-tricarboxylate (413 mg) was added a 4 M solution (4.00 mL) of hydrogen chloride in 1,4-dioxane, followed by stirring at room temperature overnight. The reaction suspension was concentrated under reduced pressure, and the residue was dried under reduced pressure to obtain dibenzyl (3R)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylate hydrochloride (358 mg).

Preparation Example 13

[0101] To a solution of 6-hydroxy-1-benzothiophene-3-carboxylic acid (100 mg), tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (186 mg), and N,N-diisopropylethylamine (88.2 μL) in N,N-dimethylformamide (3.00 mL) was added (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylaminomorpholinocarbenium hexafluorophosphate (243 mg), followed by stirring at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, and the organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-({(2-tert-butoxy-2-oxoethyl)[(6-hydroxy-1-benzothiophen-3-yl)carbonyl]amino}methyl)thiophene-2-carboxylate (230 mg).

Preparation Example 14

[0102] To a solution of tert-butyl [4-(aminomethyl)phenyl]acetate (1.00 g) in acetonitrile (15.0 mL) were added triethylamine (693 μL) and tert-butyl bromoacetate (668 μL), followed by stirring at room temperature for 4 hours. The reaction liquid was concentrated under reduced pressure, and then ethyl acetate was added thereto. The organic layer was sequentially washed with 0.1 M hydrochloric acid, an aqueous saturated sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl N-[4-(2-tert-butoxy-2-oxoethyl)benzyl]glycinate (747 mg).

Preparation Example 15

[0103] To a solution of 6-hydroxy-1-naphthoic acid (190 mg) in N,N-dimethylformamide (2.85 mL) were added tert-butyl 4-({[(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino}methyl)thiophene-2-carboxylate (345 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (422 mg), and N,N-diisopropylethylamine (190 μL), followed by stirring at 50°C for 19 hours. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-({[(2R)-1-tert-butoxy-1-oxopropan-2-yl](6-hydroxy-1-naphthoyl)amino}methyl)thiophene-2-carboxylate (101 mg).

Preparation Example 16

[0104] To a solution of N-[(benzyloxy)carbonyl]-4-(tert-butoxycarbonyl)-L-phenylalanine (500 mg) in tetrahydrofuran (4.00 mL) and tert-butyl alcohol (4.00 mL) were added di-tert-butyl dicarbonate ester (656 mg) and 4-dimethylaminopyridine (30.6 mg), followed by stirring at room temperature overnight. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was sequentially washed with water, an aqueous saturated sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain tert-butyl N-[(benzyloxy)carbonyl]-4-(tert-butoxycarbonyl)-L-phenylalaninate (641 mg).

Preparation Example 17

[0105] To a solution of (6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid (150 mg), tert-butyl N-(2-tert-butoxy-2-oxoethyl)-L-phenylalaninate (293 mg), and N,N-diisopropylethylamine (147 μL) in N,N-dimethylformamide (4.50 mL) was added (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylaminomorpholinocarbenium hexafluorophosphate (368 mg), followed by stirring at 60°C for 8 hours. The reaction mixture was diluted with ethyl acetate, and the organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl N-(2-tert-butoxy-2-oxoethyl)-N-[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetyl]-L-phenylalaninate (347 mg).

Preparation Example 18

[0106] To a solution of 5-methyl-1-benzothiophene-2-carboxylic acid (1.50 g) in N,N-dimethylformamide (10.5 mL) was added 1,1'-carbonylbis-1H-imidazole (1.27 g), followed by stirring at room temperature for 2 hours and 30 minutes. To the reaction mixture were added tert-butyl alcohol (1.44 mL) and 1,8-diazabicyclo[5.4.0]undeca-7-ene (1.17 mL), followed by stirring at 50°C for 24 hours. The reaction mixture was diluted with ethyl acetate, and then the organic layer was sequentially washed with 0.1 M hydrochloric acid and a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 5-methyl-1-benzothiophene-2-carboxylate (1.78 g).

Preparation Example 19

[0107] To a mixture of tert-butyl 5-methyl-1-benzothiophene-2-carboxylate (1.77 g), carbon tetrachloride (17.7 mL), and N-bromosuccinimide (2.16 g) was added 2,2'-azobis(isobutyronitrile) (58.5 mg), followed by stirring at 90°C overnight. The reaction suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 5-(bromomethyl)-1-benzothiophene-2-carboxylate (1.51 g).

Preparation Example 20

[0108] To a solution of tert-butyl 5-(bromomethyl)-1-benzothiophene-2-carboxylate (1.00 g) in N,N-dimethylformamide (10.0 mL) were added tert-butyl glycinate hydrochloride (1.02 g) and triethylamine (1.70 mL), followed by stirring at 85°C to 95°C overnight. The reaction mixture was cooled to room temperature, followed by extraction with ethyl acetate. The organic layer was washed with a 25% aqueous ammonium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 5-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}-1-benzothiophene-2-carboxylate (359 mg).

Preparation Example 21

[0109] To a solution of 2-tert-butyl 3-methyl (3R)-7-hydroxy-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (1.00 g) in dichloromethane (20.0 mL) were added trifluoromethane sulfonic acid anhydride (770 μL) and 2,6-dimethyl pyridine (800 μL) under ice-cooling, followed by stirring for 2 hours under ice-cooling. To the reaction mixture was added water, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. To the residue were added N,N-dimethylformamide (15.0 mL), methanol (3.00 mL), palladium (II) acetate (37.0 mg), 1,1'-bis(diphenylphosphino)ferrocene (90.0 mg), and triethylamine (1.10 mL), followed by stirring at 80°C overnight in a carbon monoxide atmosphere. The reaction mixture was cooled to room temperature and then

concentrated under reduced pressure. To the residue was added water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 2-tert-butyl 3,7-dimethyl (3R)-3,4-dihydroisoquinoline-2,3,7(1H)-tricarboxylate (350 mg).

Preparation Example 22

[0110] To a solution of (3R)-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid (320 mg) in N,N-dimethylformamide (6.00 mL) were added potassium carbonate (315 mg) and benzyl bromide (275 μL), followed by stirring at room temperature overnight. To the reaction suspension was added water, followed by extraction with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 3,7-dibenzyl 2-tert-butyl (3R)-3,4-dihydroisoquinoline-2,3,7(1H)-tricarboxylate (415 mg).

Preparation Example 23

[0111] To a solution of 2-bromo-1,3,5-trimethylbenzene (925 μL) in tetrahydrofuran (20.0 mL) was added dropwise a 1.59 M solution (3.86 mL) of n-butyllithium in hexane at -78°C, followed by stirring at -78°C for 30 minutes. To the reaction mixture was added dropwise a solution of tert-butyl (4-bromo-2-thienyl)acetate (1.55 g) in tetrahydrofuran (15.0 mL), followed by stirring at-78°C for 30 minutes. Subsequently, to the reaction mixture was added dropwise a 1.59 M solution (3.51 mL) of n-butyllithium in hexane, followed by stirring at -78°C for 30 minutes. To the reaction mixture was added dropwise N,N-dimethylformamide (451 μL), followed by stirring at 78°C for 1 hour. To the reaction liquid were added an aqueous ammonium chloride solution and ethyl acetate, thereby extracting the organic layer. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl (4-formyl-2-thienyl)acetate (355 mg).

Preparation Example 24

[0112] To a solution of tert-butyl (4-formyl-2-thienyl)acetate (350 mg), tert-butyl glycinate (243 mg), and acetic acid (265 μL) in dichloromethane (4.05 mL) was added sodium triacetoxyborohydride (656 mg) under ice-cooling, followed by stirring at room temperature for 3 hours. The reaction mixture was neutralized by the addition of an aqueous saturated sodium hydrogen carbonate solution, and then extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl N-{[5-(2-tert-butoxy-2-oxoethyl)-3-thienyl]methyl}glycinate (237 mg).

Preparation Example 25

[0113] A mixture of tert-butyl [3-(aminomethyl)phenyl]acetate (1.00 g), tert-butyl bromoacetate (700 μL), potassium carbonate (650 mg), and acetonitrile (20.0 mL) was stirred at room temperature overnight. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl N-[3-(2-tert-butoxy-2-oxoethyl)benzyl]glycinate (1.14 g).

Preparation Example 26

[0114] To a mixture of N-benzyl-N-(cyclopenta-3-en-1-ylmethyl)-2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (430 mg), potassium carbonate (174 mg), and N,N-dimethylformamide (4.30 mL) was added benzyl bromide (177 μL), followed by stirring at 50°C for 6 hours. The reaction mixture was cooled, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain N-benzyl-2-[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]-N-(cyclopenta-3-en-1-ylmethyl)acetamide (416 mg).

Preparation Example 27

[0115] To a mixture of N-benzyl-2-[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]-N-(cyclopenta-3-en-1-ylmethyl)acetamide (100 mg), tert-butyl alcohol (2.40 mL), and water (600 μL) were added a 2.5% solution (269 μL) of osmium

tetraoxide in tert-butyl alcohol, and 4-methylmorpholine 4-oxide (75.5 mg), followed by stirring at room temperature for 2 hours. To the reaction mixture was added an aqueous sodium thiosulfate solution, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain N-benzyl-2-[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]-N-[(3,4-dihydroxycyclopentyl)methyl]acetamide (107 mg).

Preparation Example 28

[0116] To a mixture of N-benzyl-2-[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]-N-[(3,4-dihydroxycyclopentyl)methyl]acetamide (106 mg), iodobenzene diacetate (322 mg), dichloromethane (3.00 mL), and water (1.00 mL) was added 1-methyl-2-azaadamantan-N-oxyl (3.33 mg), followed by stirring at room temperature for 3 hours. To the reaction mixture was added a 20% aqueous sodium thiosulfate solution, followed by stirring at room temperature for 5 minutes. Subsequently, 1 M hydrochloric acid was added thereto, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 3-[(benzyl{[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]pentanedioic acid (110 mg).

Preparation Example 29

[0117] To a mixture of a (1S)-1-phenylethanamine salt (370 mg) of [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof, and ethyl acetate (4.50 mL) was added 3 M hydrochloric acid (4.50 mL), followed by stirring at room temperature for 2 hours. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (243 mg).

Preparation Example 30

[0118] To a mixture of a (1R)-1-phenylethanamine salt (450 mg) of [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof, and ethyl acetate (5.51 mL) was added a 4 M solution (4.13 mL) of hydrogen chloride in ethyl acetate, followed by stirring at room temperature for 2 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (290 mg).

Preparation Example 31

[0119] To a solution of [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (238 mg) obtained in Preparation Example 29 in dichloromethane (8.00 mL) was added a 1 M solution (2.20 mL) of boron tribromide in dichloromethane under ice-cooling, followed by stirring at room temperature for 2 hours. To the reaction mixture was added ice-water, followed by extraction with ethyl acetate. The organic layer was washed with water, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain [(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (147 mg).

Preparation Example 32

[0120] To a solution of [(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (288 mg) obtained in Preparation Example 30 in dichloromethane (9.77 mL) was added dropwise a 1 M solution (2.66 mL) of boron tribromide in dichloromethane under ice-cooling, followed by stirring at room temperature for 2 hours. To the reaction mixture was added ice-water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain [(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (230 mg).

Preparation Example 33

[0121] To a solution of [(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (145 mg) obtained in Preparation Example 31 in N,N-dimethylformamide (2.90 mL) were added tert-butyl 4-({[(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino}methyl)thiophene-2-carboxylate (255 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (295 mg), and N,N-diisopropylethylamine (135 μL), followed by stirring at room

temperature overnight. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with water, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-[([(2R)-1-tert-butoxy-1-oxopropan-2-yl]{[(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (237 mg).

Preparation Example 34

[0122] To a solution of tert-butyl 4-[([(2R)-1-tert-butoxy-1-oxopropan-2-yl]{[(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (235 mg) obtained in Preparation Example 33 in dichloromethane (3.00 mL) were added N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (115 mg), 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (220 mg), and 4-dimethylaminopyridine (18.0 mg), followed by stirring at room temperature for 3 hours. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with water, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-[({[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} [(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (325 mg).

Preparation Example 35

[0123] To a solution of [(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetic acid or an enantiomer thereof (228 mg) obtained in Preparation Example 32 in N,N-dimethylformamide (4.56 mL) were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (504 mg), N,N-diisopropylethylamine (227 μL), and tert-butyl 4-({[(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino}methyl)thiophene-2-carboxylate (453 mg), followed by stirring at room temperature overnight. The reaction solution was diluted with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-[([(2R)-1-tert-butoxy-1-oxopropan-2-yl]{[(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (330 mg).

Preparation Example 36

[0124] To a mixture of tert-butyl 4-[([(2R)-1-tert-butoxy-1-oxopropan-2-yl]{[(1R)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (328 mg) obtained in Preparation Example 35, 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (282 mg), 4-dimethylaminopyridine (22.7 mg), and dichloromethane (4.92 mL) was added N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (154 mg), followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-[({[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} [(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (460 mg).

Preparation Example 37

[0125] tert-Butyl 3-{[{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate (395 mg) was preparatively purified by a supercritical chromatography method (carbon dioxide-methanol) by means of a UV trigger, and then concentrated under reduced pressure to obtain PEx. 37-1 (188 mg, RT: 4.02 min) and PEx. 37-2 (187 mg, RT: 4.87 min) as the tert-butyl 3-{[{[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate and an enantiomer thereof. Further, the analysis conditions for the supercritical chromatography method carried out to determine RT are shown below.

Column: CHIRALCEL OZ-H/SFC 4.6 mm I.D. × 250 mm (particle diameter: 5 μm), manufactured by Daicel Chemical Industries, Ltd.
Mobile phase: carbon dioxide 65%, methanol 35%
Flow rate: 3 mL/min (6 min)
Detection wavelength: 220 nm to 300 nm

Column temperature: 40°C
Discharge pressure: 100 bar

Preparation Example 38

[0126] A mixture of 6-hydroxy-1-naphthoic acid (150 mg), tert-butyl 4-(tert-butoxycarbonyl)-L-phenylalaninate (200 mg), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (160 mg), 1H-benzotriazol-1-ol (110 mg), and N,N-dimethylformamide (4.00 mL) was stirred at room temperature overnight. To the reaction mixture was added water, followed by stirring for 1 hour. The precipitate was collected by filtration, washed with water, and then dried under reduced pressure to obtain tert-butyl 4-(tert-butoxycarbonyl)-N-(6-hydroxy-1-naphthoyl)-L-phenylalaninate (183 mg).

Preparation Example 39

[0127] A mixture of tert-butyl 4-(tert-butoxycarbonyl)-N-(6-hydroxy-1-naphthoyl)-L-phenylalaninate (180 mg), 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (180 mg), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (90.0 mg), 4-dimethylaminopyridine (15.0 mg), and dichloromethane (2.00 mL) was stirred at room temperature for 2 hours. The reaction mixture was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl N-[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1-naphthoyl]-4-(tert-butoxycarbonyl)-L-phenylalaninate (303 mg).

Preparation Example 40

[0128] To a solution of 6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (200 mg) in N,N-dimethylformamide (3.00 mL) were added tert-butyl 4-{[(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (341 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (435 mg), and N,N-diisopropylethylamine (196 μL), followed by stirring at room temperature for 2 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-({(2-tert-butoxy-2-oxoethyl)[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]amino}methyl)thiophene-2-carboxylate (522 mg).

Preparation Example 41

[0129] To a solution of tert-butyl 4-({(2-tert-butoxy-2-oxoethyl)[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)carbonyl]amino}methyl)thiophene-2-carboxylate (520 mg) in dichloromethane (10.4 mL) were added 4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoic acid (433 mg), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (298 mg), and 4-dimethylaminopyridine (38.0 mg) under ice-cooling, followed by stirring at room temperature for 2 hours. To the reaction solution were added water and 1 M hydrochloric acid, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain tert-butyl 4-{[{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (723 mg).

Preparation Example 42

[0130] To a solution of (3R)-2-(tert-butoxycarbonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.50 g) in toluene (60.0 mL), and methanol (9.00 mL) was added dropwise a 0.60 M solution (10.0 mL) of trimethylsilyldiazomethane in hexane, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added acetic acid (300 μL), and then an aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was sequentially washed with water and a saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-ethyl acetate) to obtain 2-tert-butyl 3-methyl (3R)-7-hydroxy-3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (1.47 g).

Preparation Example 43

[0131] To a solution of dibenzyl (3R)-2-{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylate (257 mg) in ethanol (5.00 mL) was

added 10% palladium-carbon (52.0 mg, 50% wet product), followed by stirring at room temperature for 2 hours at normal pressure in a hydrogen atmosphere. The reaction mixture was filtered by passing it through a Celite (registered trademark) layer, and then the filtrate was concentrated under reduced pressure to obtain (3R)-2-{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid (213 mg).

Preparation Example 44

[0132] A mixture of di-tert-butyl 3-[(benzyl{[6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}amino)methyl]pentanedioate (230 mg), 10% palladium-carbon (38.1 mg, 50% wet product), and methanol (4.60 mL) was stirred at room temperature for 16 hours at normal pressure in a hydrogen atmosphere. The reaction mixture was filtered by passing it through a Celite (registered trademark) layer, and then the filtrate was concentrated under reduced pressure to obtain di-tert-butyl 3-({benzyl[(6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetyl]amino}methyl)pentanedioate (186 mg).

Example 1

[0133] To tert-butyl 4-({[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-2-naphthoyl](2-tert-butoxy-2-oxoethyl)amino}methyl)thiophene-2-carboxylate (132 mg) was added a 4 M solution (2.02 mL) of hydrogen chloride in 1,4-dioxane, followed by stirring at room temperature for 24 hours. The reaction suspension was concentrated under reduced pressure, and then the residue was purified by octadecylsilyl (hereinafter referred to as ODS) column chromatography (0.01 M hydrochloric acid-acetonitrile) to obtain 4-{[{6-[(4-carbamimidamidobenzoyl)oxy]-2-naphthoyl}(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid monohydrochloride (62.7 mg).

Example 2

[0134] To a solution of tert-butyl 3-{[{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate (528 mg) in dichloromethane (5.00 mL) was added trifluoroacetic acid (2.00 mL), followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (606 μL) and acetonitrile (10.0 mL), followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) and dried under reduced pressure to obtain 3-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid monohydrochloride (227 mg).

Example 3

[0135] To a solution of tert-butyl N-[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1-naphthoyl]-4-(tert-butoxycarbonyl)-L-phenylalaninate (300 mg) in dichloromethane (1.50 mL) was added trifluoroacetic acid (1.50 mL), followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (1.00 mL) and acetonitrile (1.00 mL), followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) to obtain N-{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}-4-carboxy-L-phenylalanine monohydrochloride (158 mg).

Example 4

[0136] To a solution of tert-butyl 4-{[{[6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl}(2-tert-butoxy-2-oxoethyl)amino]methyl}thiophene-2-carboxylate (720 mg) in dichloromethane (5.33 mL) was added trifluoroacetic acid (5.36 mL), followed by stirring at room temperature for 5 hours. To the reaction mixture was added acetonitrile, followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) to obtain 4-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}carbonyl)(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid monohydrochloride (440 mg).

Example 5

[0137] To a solution of tert-butyl 3-{[{[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} (2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate or an enantiomer thereof

(PEx. 37-1, 181 mg) obtained in Preparation Example 37 in dichloromethane (3.00 mL) was added trifluoroacetic acid (686 μL), followed by stirring at room temperature for 4 hours. The reaction solution was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (208 μL) and acetonitrile (10.0 mL), followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) and dried under reduced pressure to obtain a monohydrochloride (91 mg, RT 10.6 min) of 3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid or an enantiomer thereof. Further, the analysis conditions for the chiral column chromatography method carried out to determine RT are shown below.

Column: CHIRALPAK IE-3 4.6 mm I.D. × 250 mm (particle diameter: 3 μm), manufactured by Daicel Chemical Industries, Ltd.
Mobile phase: hexane (containing 0.1% trifluoroacetic acid) 60%, ethanol (containing 0.1% trifluoroacetic acid) 40%
Flow rate: 1 mL/min
Detection wavelength: 254 nm
Column temperature: 40°C

Example 6

[0138] To a solution of tert-butyl 3-{[{[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} (2-tert-butoxy-2-oxoethyl)amino]methyl}benzoate or an enantiomer thereof (PEx. 37-2, 183 mg) obtained in Preparation Example 37 in dichloromethane (3.03 mL) was added trifluoroacetic acid (693 μL), followed by stirring at room temperature for 4 hours. The reaction solution was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (210 μL) and acetonitrile (10.0 mL), followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) and dried under reduced pressure to obtain a monohydrochloride (98 mg, RT 14.1 min) of 3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid or an enantiomer thereof. Further, the analysis conditions for the chiral column chromatography method carried out to determine RT are shown below.

Column: CHIRALPAK IE-3 4.6 mm I.D. × 250 mm (particle diameter: 3 μm), manufactured by Daicel Chemical Industries, Ltd.
Mobile phase: hexane (containing 0.1% trifluoroacetic acid) 60%, ethanol (containing 0.1% trifluoroacetic acid) 40%
Flow rate: 1 mL/min
Detection wavelength: 254 nm
Column temperature: 40°C

Example 7

[0139] To a solution of tert-butyl 4-[({[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl}[(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (324 mg) obtained in Preparation Example 34 in dichloromethane (3.00 mL) was added trifluoroacetic acid (1.50 mL), followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (2.00 mL) and acetonitrile (1.50 mL), followed by concentrating under reduced pressure. The residue was purified by ODS column chromatography (0.01 M hydrochloric acid-acetonitrile) to obtain hydrochloride (46 mg) of 4-({({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)[(1R)-1-carboxyethyl]amino}methyl)thiophene-2-carboxylic acid or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene.

Example 8

[0140] To a solution of tert-butyl 4-[({[(1R)-6-({4-[N',N"-bis(tert-butoxycarbonyl)carbamimidamide]benzoyl}oxy)-1,2,3,4-tetrahydronaphthalen-1-yl]acetyl} [(2R)-1-tert-butoxy-1-oxopropan-2-yl]amino)methyl]thiophene-2-carboxylate or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (460 mg) obtained in Preparation Example 36 in dichloromethane (3.07 mL) was added trifluoroacetic acid (2.06 mL), followed by stirring at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and then to the residue were added 1 M hydrochloric acid (588 μL) and acetonitrile (3.07 mL), followed by concentrating under reduced pressure. To the residue was added ethyl acetate, followed by concentrating under reduced pressure. The obtained solid was washed with acetonitrile to obtain 4-({({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)[(1R)-1-carboxyethyl]ami-

no}methyl)thiophene-2-carboxylic acid or an epimer at position 1 of the 1,2,3,4-tetrahydronaphthalene (44 mg).

Example 9

[0141] To a 50% aqueous acetonitrile solution (80.0 mL) of a monohydrochloride (3.83 g) of 3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid or an enantiomer thereof obtained in Example 6 was added dropwise a 1 M aqueous sodium hydroxide solution (6.44 mL) under ice-cooling, followed by stirring at room temperature for 3 hours. The precipitate was collected by filtration, then washed with a 50% aqueous acetonitrile solution, and dried in air for 1 hour. The dried product was suspended in a 50% aqueous acetonitrile solution (400 mL), followed by stirring at 120°C for 30 minutes. The reaction mixture was stirred at room temperature for 12 hours. The precipitate was collected by filtration, then washed with a 50% aqueous acetonitrile solution, and dried at room temperature under reduced pressure to obtain 3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid or an enantiomer thereof (2.89 g).

[0142] The compounds of Preparation Examples and Examples shown in Tables below were prepared in the same manner as in Preparation Examples and Examples as described above.

[Table 3]

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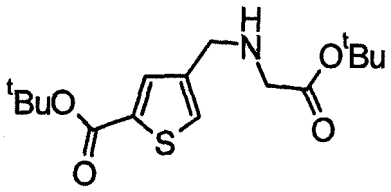
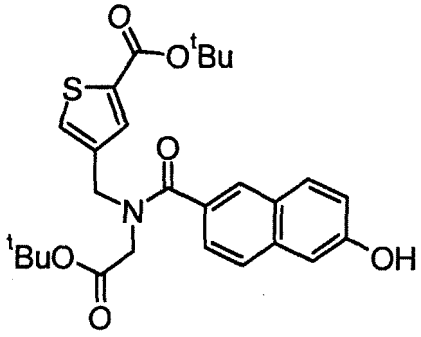
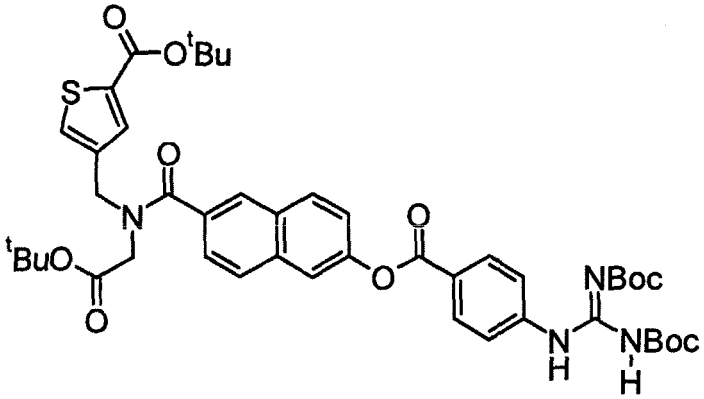
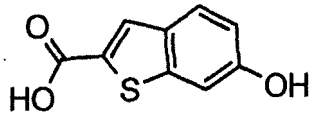
1	P1		ESI+: 328
2	P2		ESI+:520 [M+Na]+
3	P3		ESI+: 859
4	P4		ESI+: 195

(continued)

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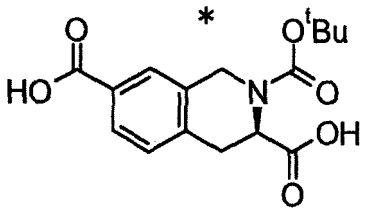
5	P5		ESI+: 344 [M+Na]+

[Table 4]

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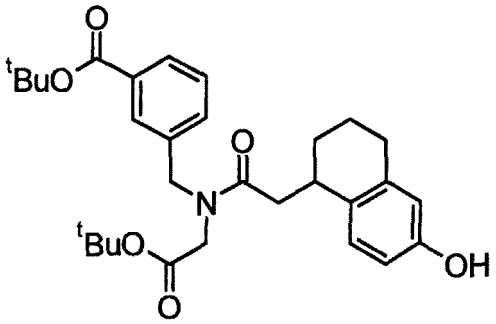
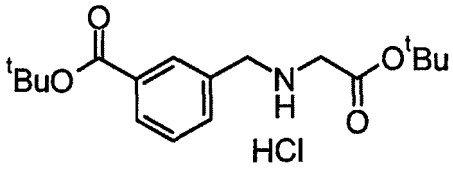
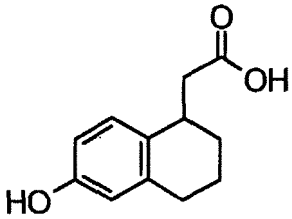
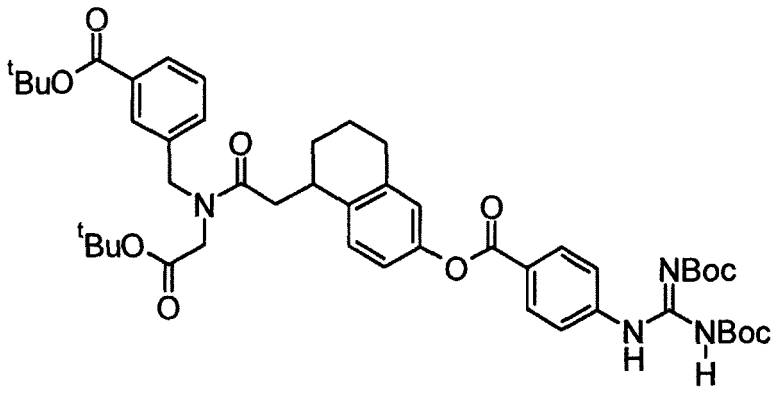
6	P6		ESI+: 532 [M+Na]+
7	P7		ESI+:322
8	P8		ESI+: 229 [M+Na]+
9	P9		ESI+: 871

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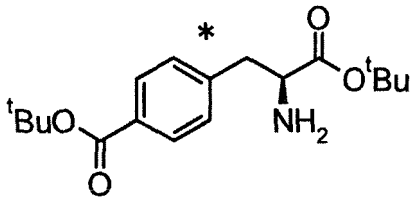
10	P10		ESI+: 322

[Table 5]

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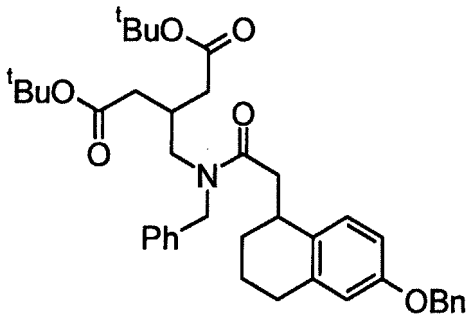
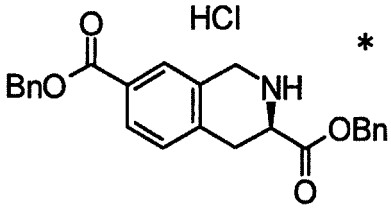
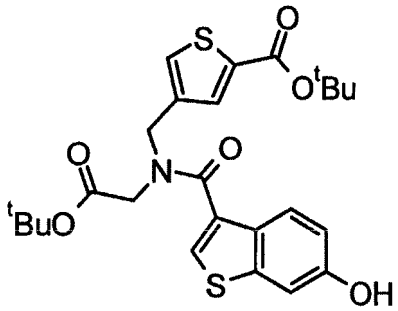
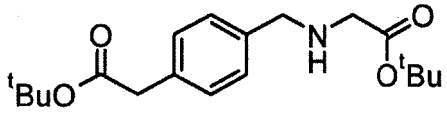
11	P11		ESI+: 664 [M+Na]+
12	P12		ESI+: 402
13	P13		ESI+: 526 [M+Na]+
14	P14		ESI+: 336

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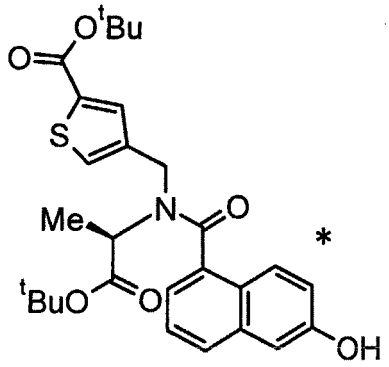
15	P15		ESI+: 534 [M+Na]+

[Table 6]

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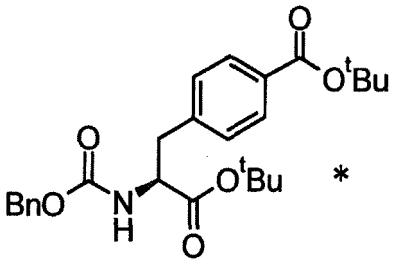
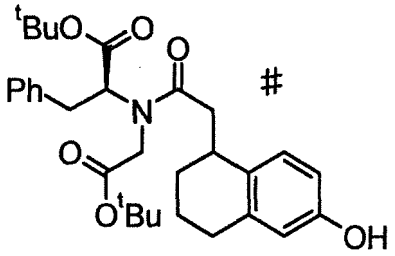
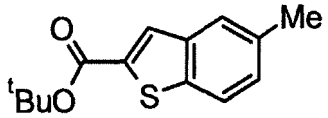
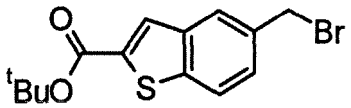
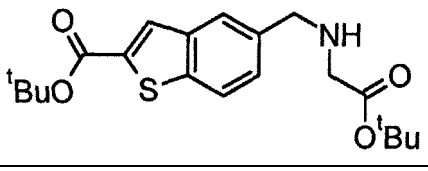
16	P16		ESI+: 478 [M+Na]+
17	P17		ESI+: 546 [M+Na]+
18	P18		ESI+: 271 [M+Na]+
19	P19		ESI+: 349 [M+Na]+
20	P20		ESI+: 378

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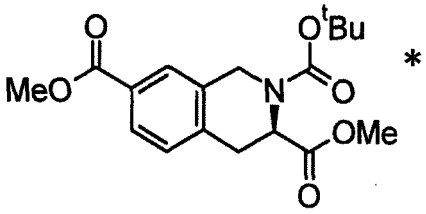
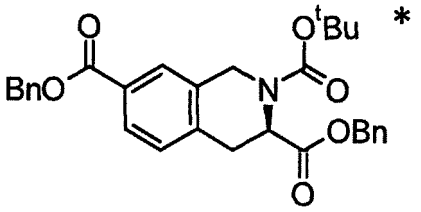
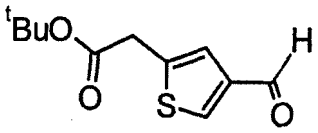
21	P21		ESI+: 372 [M+Na]+
22	P22		ESI+: 524 [M+Na]+
23	P23		ESI+: 249 [M+Na]+

[Table 7]

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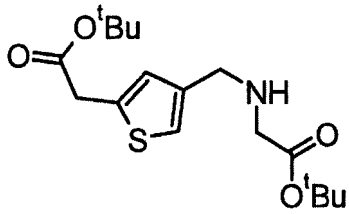
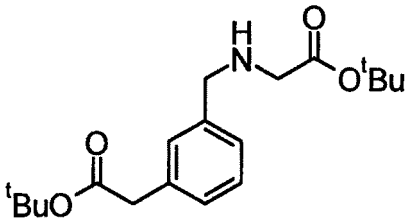
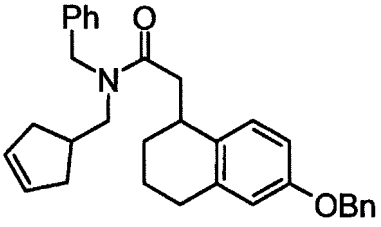
24	P24		ESI+: 342
25	P25		ESI+: 336
26	P26		ESI+: 466

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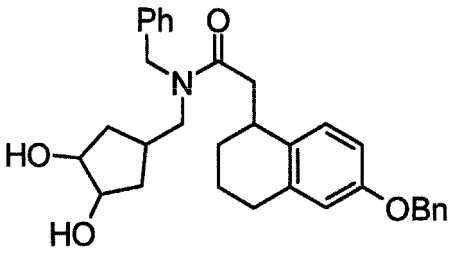
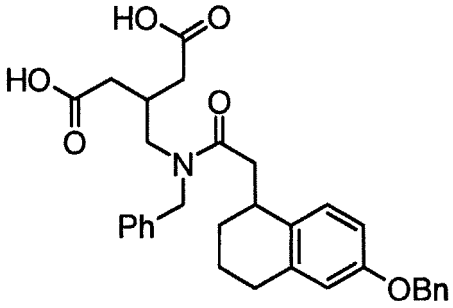
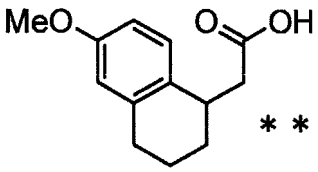
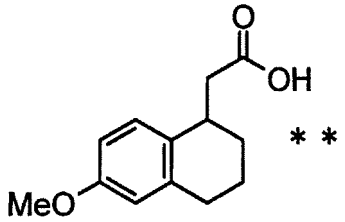
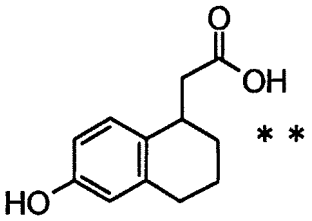
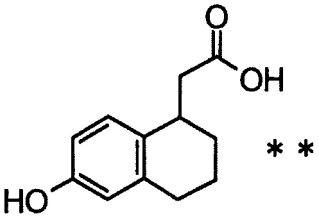
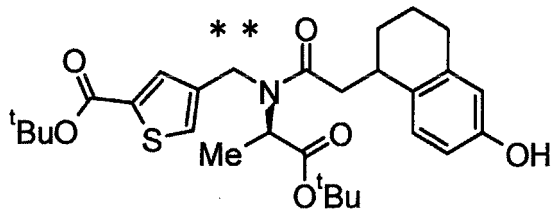
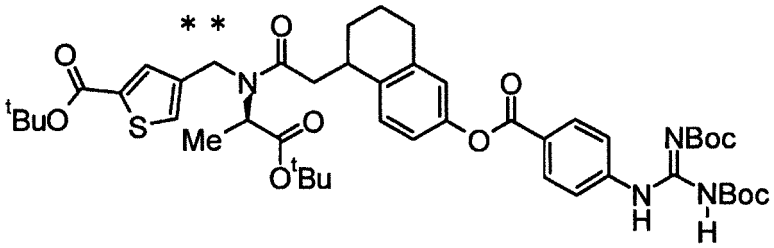
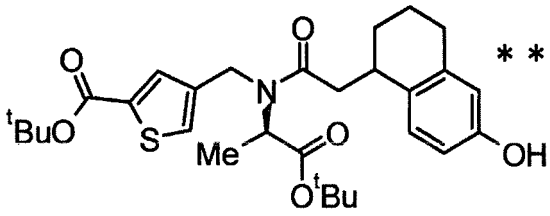
PEx	PSyn	Str	Data
27	P27		ESI+: 522 [M+Na]+
28	P28		ESI+: 530
29	P29		ESI-:219

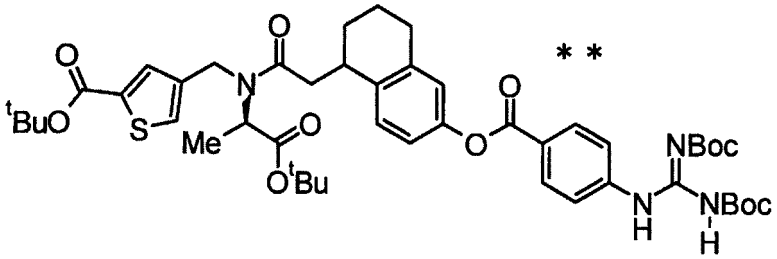
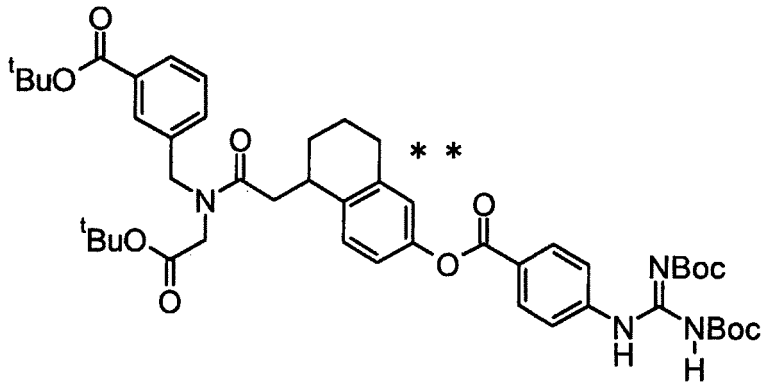
[Table 8]

PEx	PSyn	Str	Data
30	P30		ESI-:219
31	P31		ESI-:205
32	P32		ESI-:205

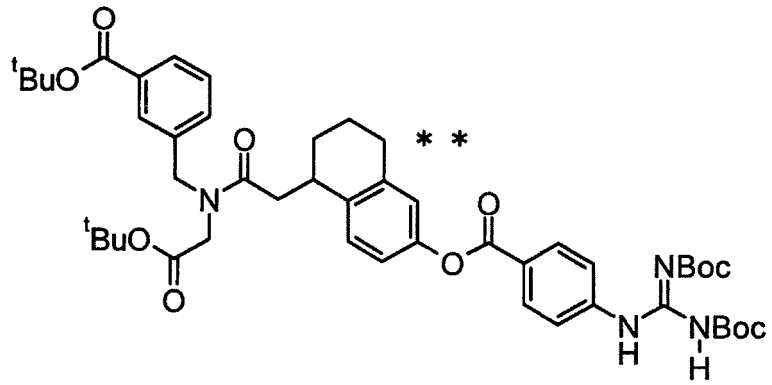
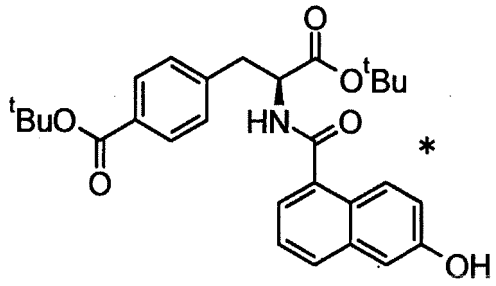
(continued)

PEx	PSyn	Str	Data
33	P33		ESI+:552 [M+Na]+
34	P34		ESI+: 891
35	P35		ESI+: 552 [M+Na]+

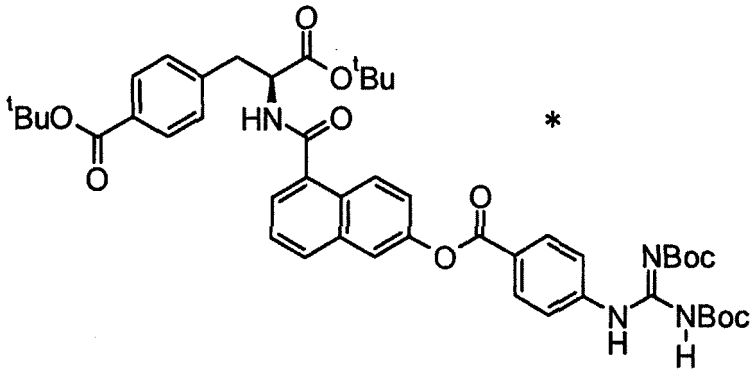
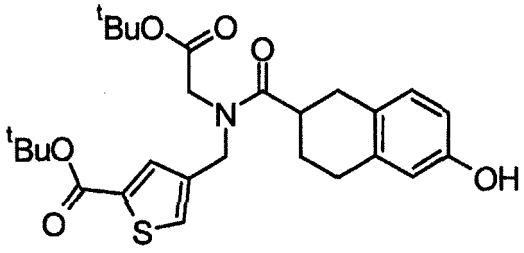
[Table 9]

PEx	PSyn	Str	Data
36	P36		ESI+: 891
37-1	P37		ESI+: 893 [M+Na]+

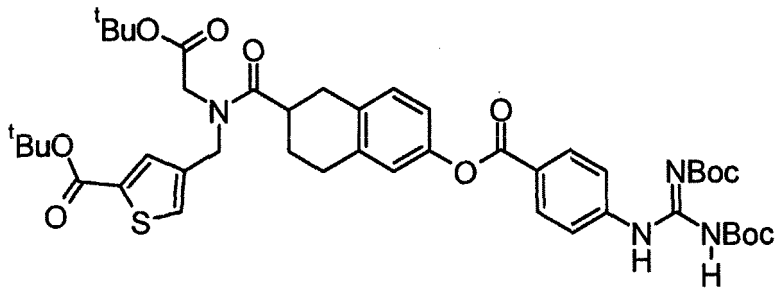
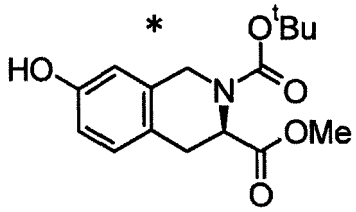
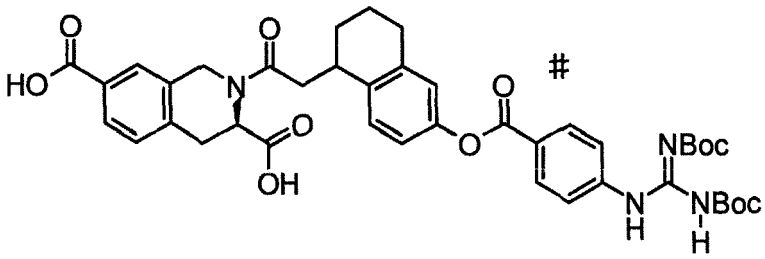
(continued)

PEx	PSyn	Str	Data
37-2	P37		ESI+: 871
38	P38		ESI+: 514 [M+Na]+

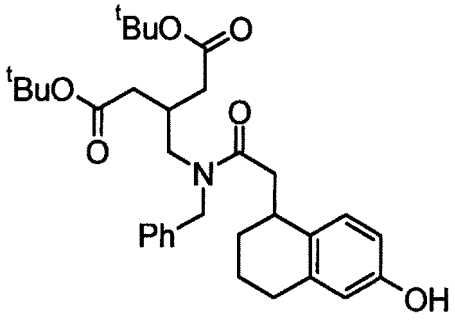
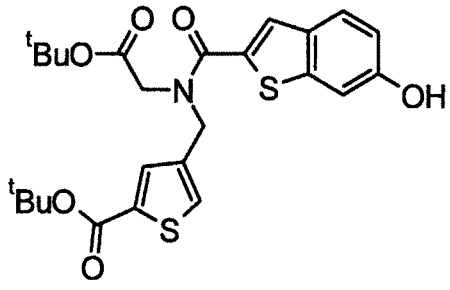
[Table 10]

PEx	PSyn	Str	Data
39	P39		ESI+: 853
40	P40		ESI+:524 [M+Na]+

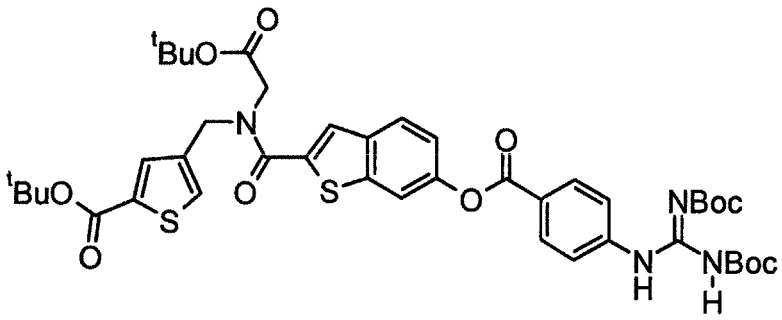
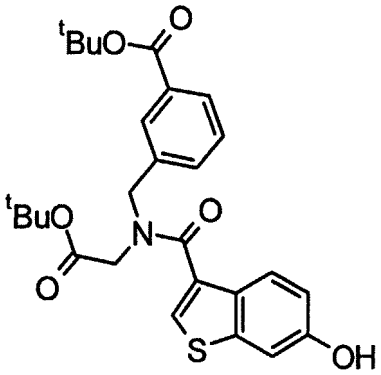
(continued)

PEx	PSyn	Str	Data
41	P41		ESI+: 863
42	P42		ESI+: 330 [M+Na]+
43	P43		ESI+: 771

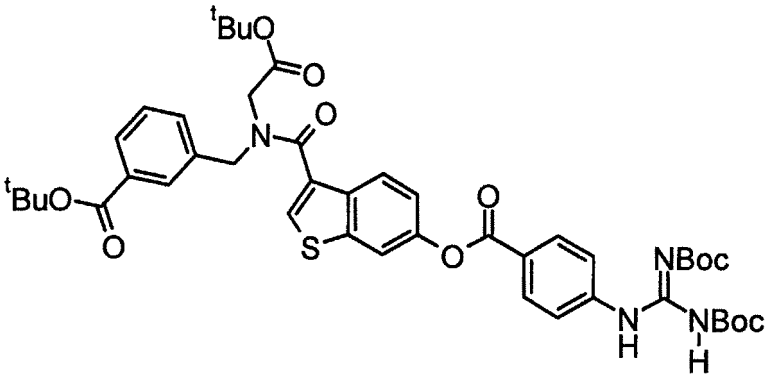
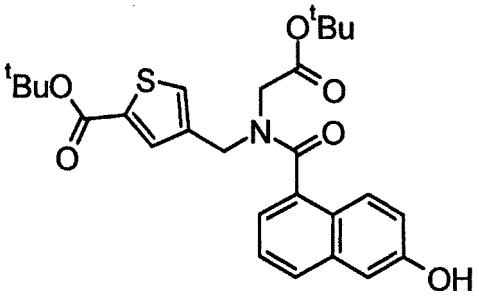
[Table 11]

PEx	PSyn	Str	Data
44	P44		ESI+: 574 [M+Na]+
45	P2		ESI+: 526 [M+Na]+

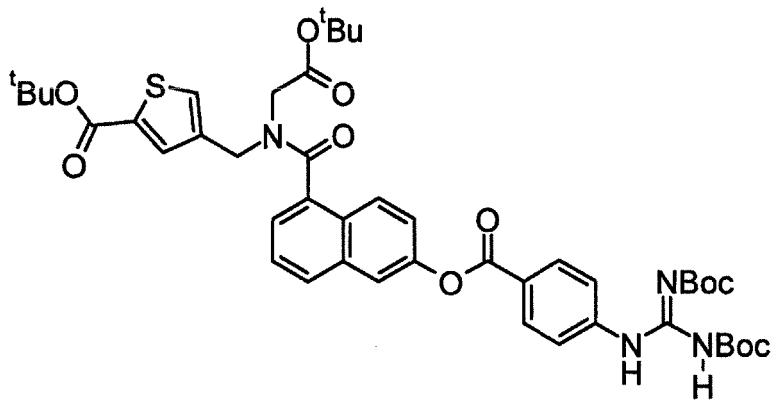
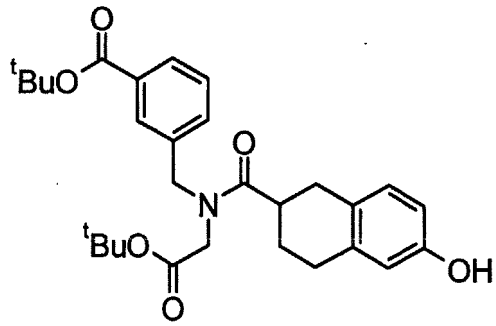
(continued)

PEx	PSyn	Str	Data
46	P3		ESI+: 865
47	P6		ESI+: 520 [M+Na]+

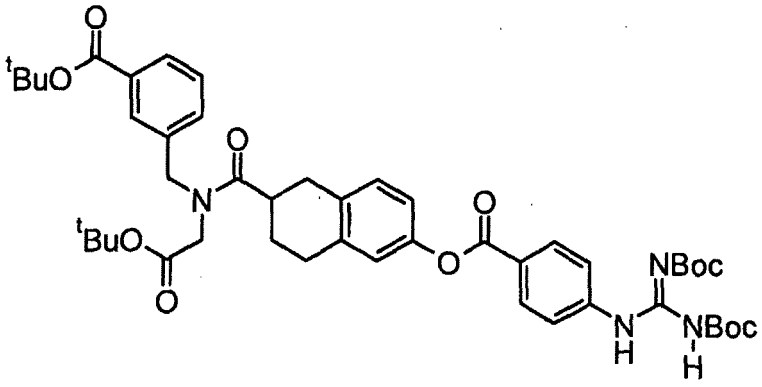
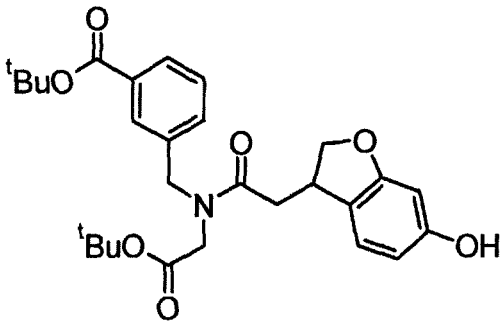
[Table 12]

PEx	PSyn	Str	Data
48	P3		ESI+: 859
49	P2		ESI+:520 [M+Na]+

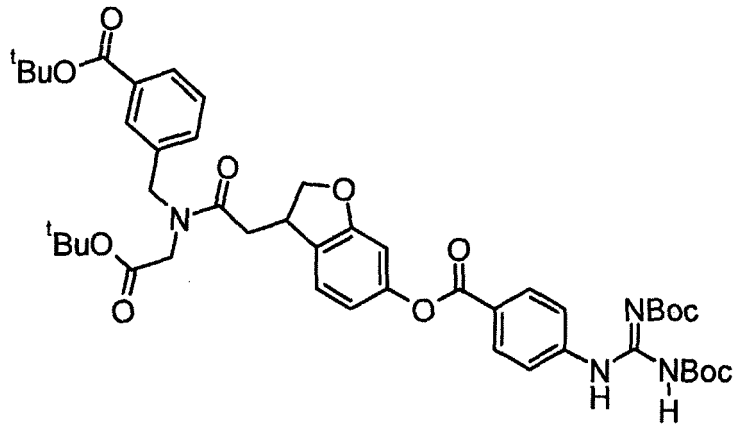
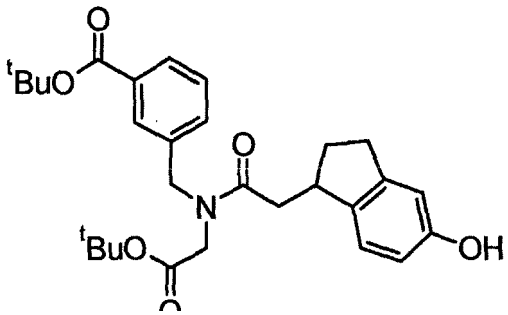
(continued)

PEx	PSyn	Str	Data
50	P3		ESI+: 859
51	P2		ESI+: 518 [M+Na]+

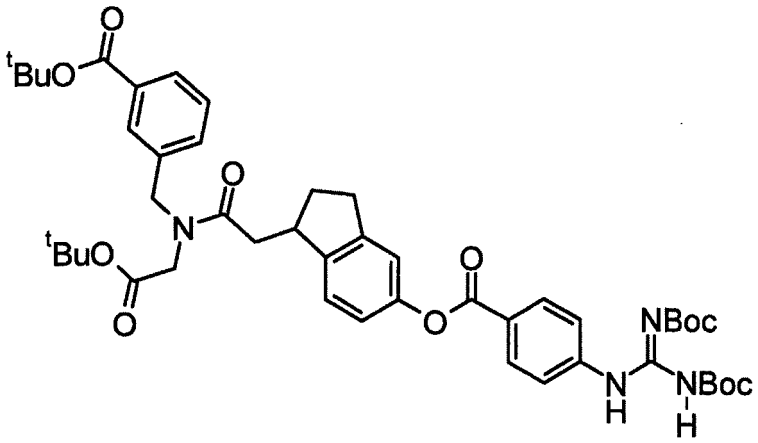
[Table 13]

PEx	PSyn	Str	Data
52	P3		ESI+: 879 [M+Na]+
53	P2		ESI+: 520 [M+Na]+

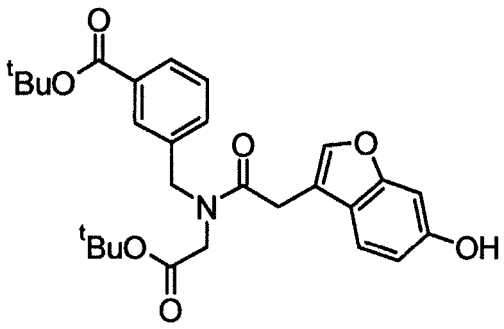
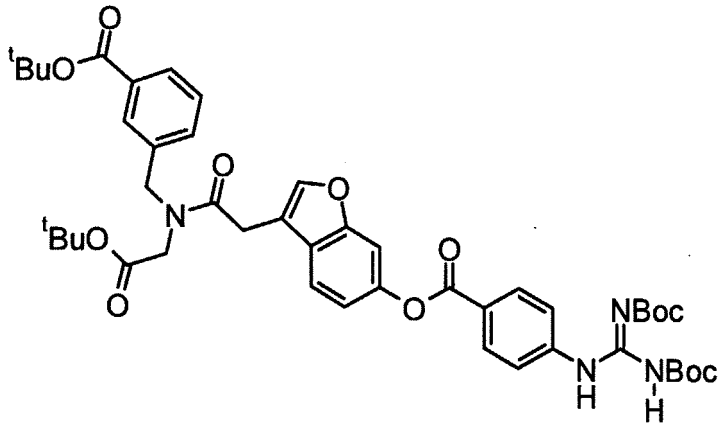
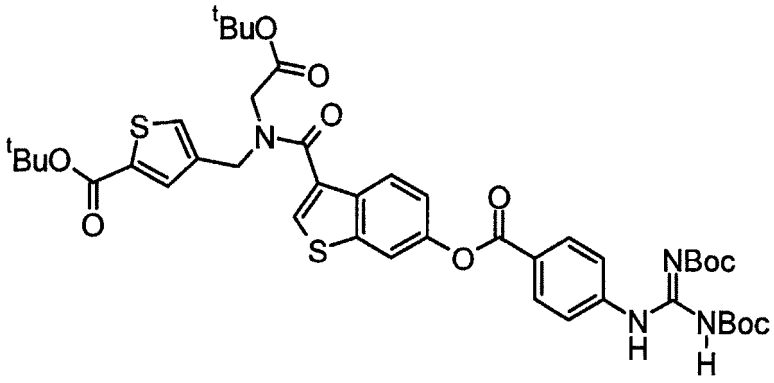
(continued)

PEx	PSyn	Str	Data
54	P3		ESI+:881 [M+Na]+
55	P2		ESI+: 518 [M+Na]+

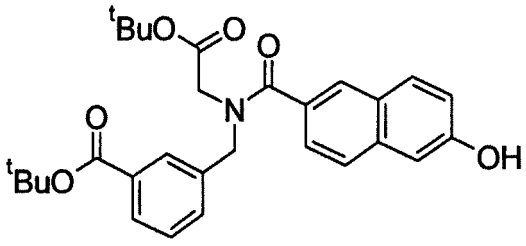
[Table 14]

PEx	PSyn	Str	Data
56	P3		ESI+: 857

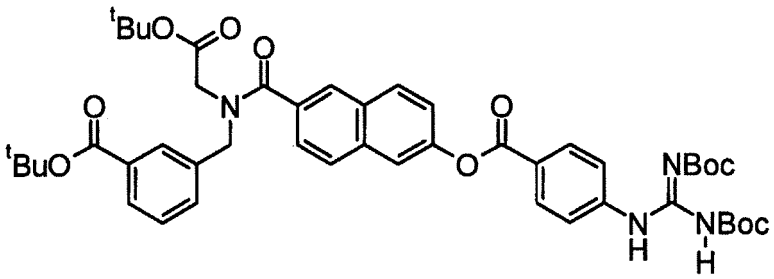
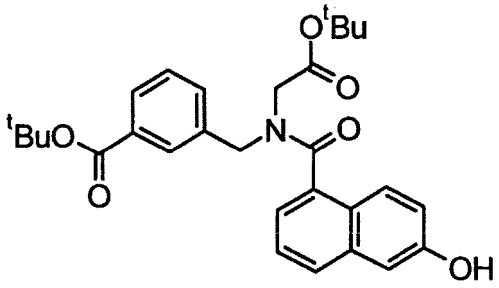
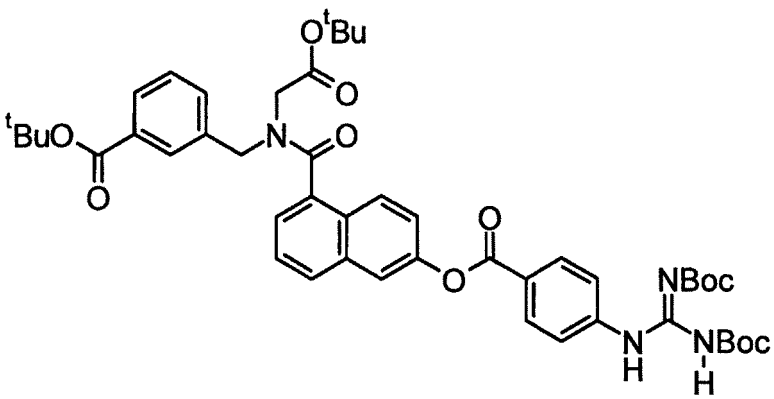
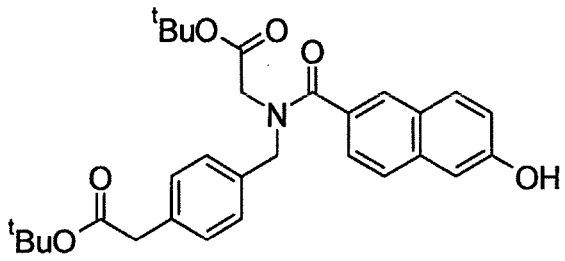
(continued)

PEx	PSyn	Str	Data
57	P2		ESI+: 518 [M+Na]+
58	P3		ESI+: 879 [M+Na]+
59	P3		ESI+: 887 [M+Na]+

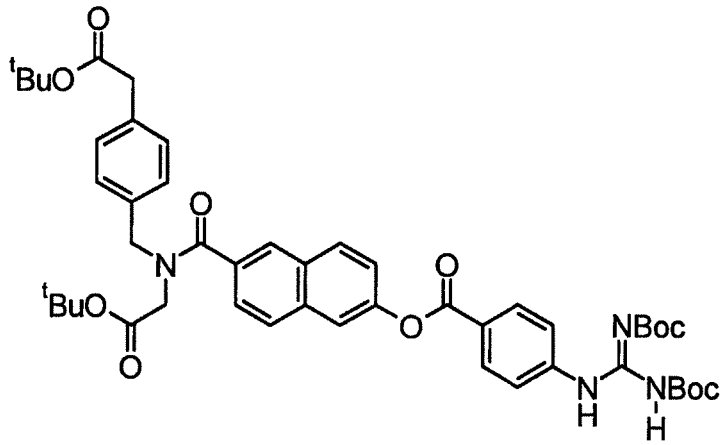
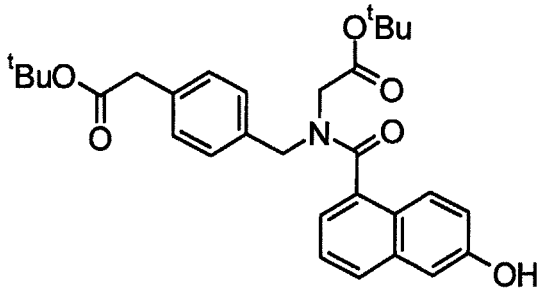
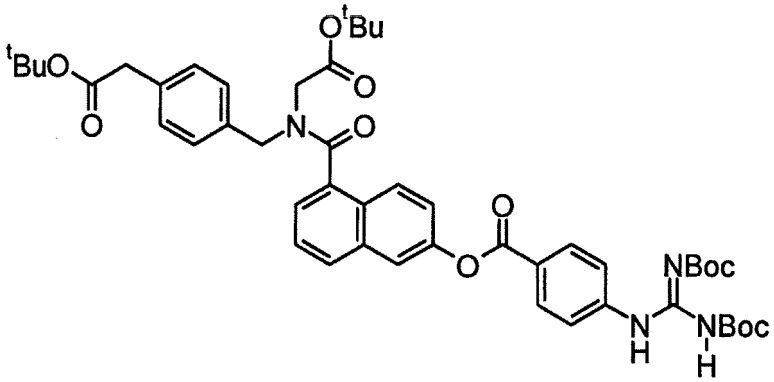
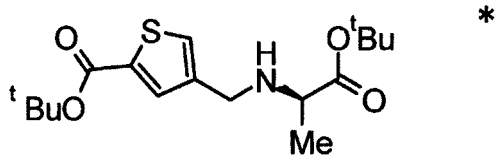
[Table 15]

PEx	PSyn	Str	Data
60	P2		ESI+: 514 [M+Na]+

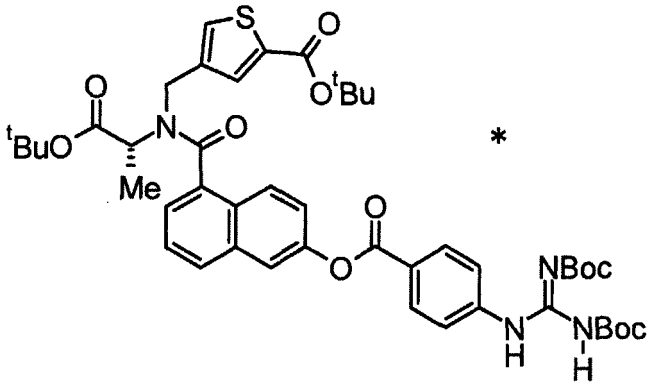
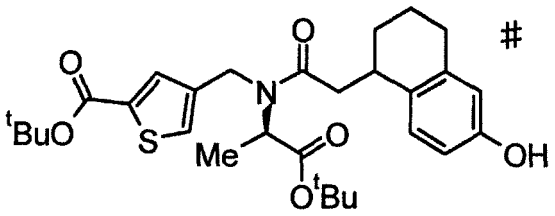
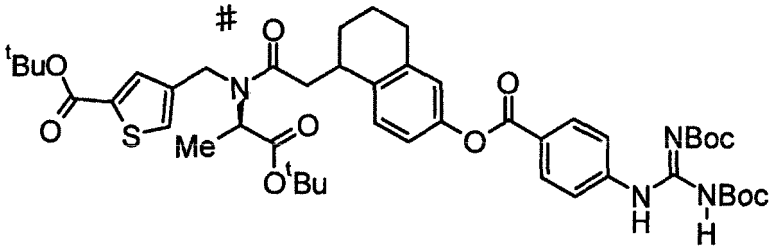
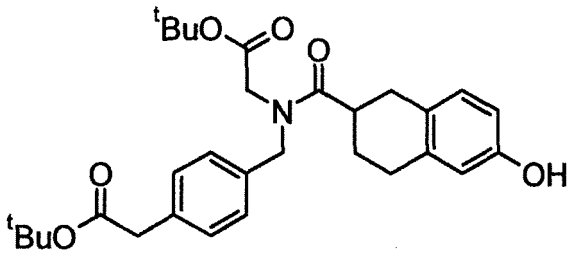
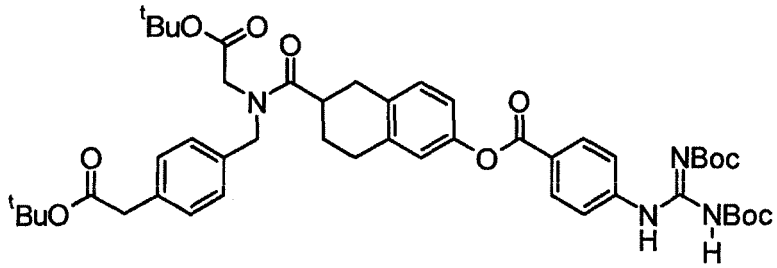
(continued)

PEx	PSyn	Str	Data
61	P3		ESI+: 875 [M+Na]+
62	P2		ESI+: 514 [M+Na]+
63	P3		ESI+: 875 [M+Na]+
64	P2		ESI+: 528 [M+Na]+

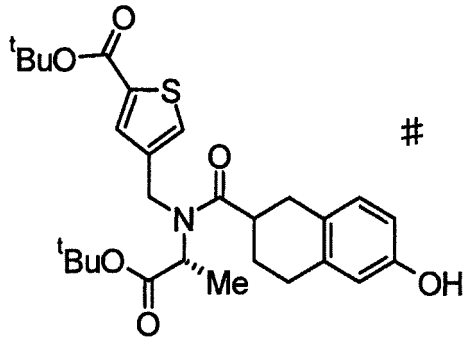
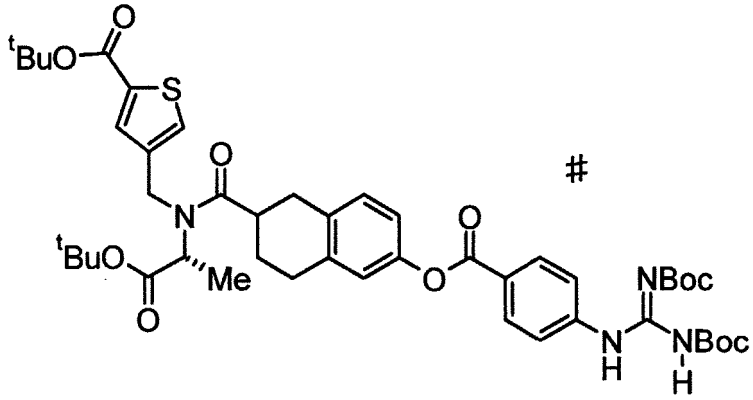
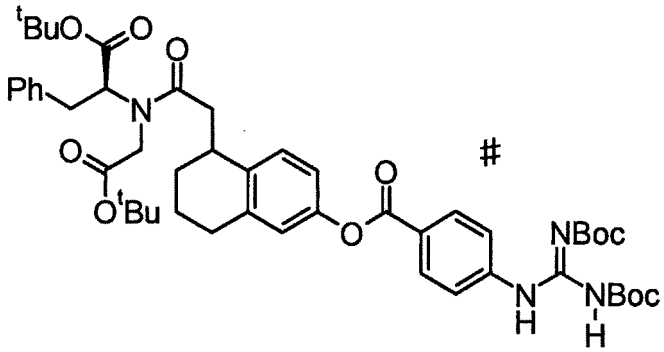
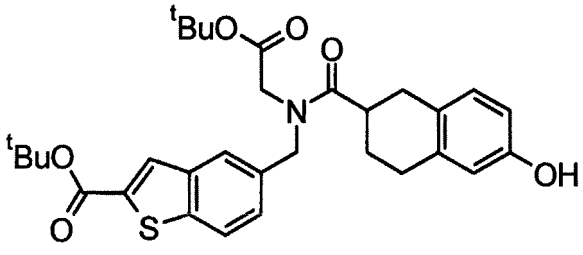
[Table 16]

PEx	PSyn	Str	Data
65	P3		ESI+: 867
66	P2		ESI+: 528 [M+Na]+
67	P3		ESI+: 867
68	P1		ESI+: 342

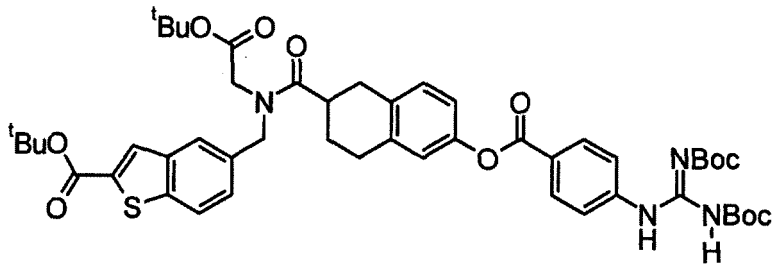
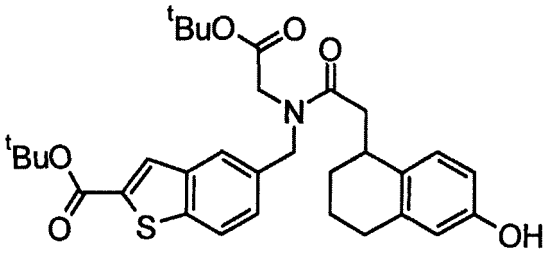
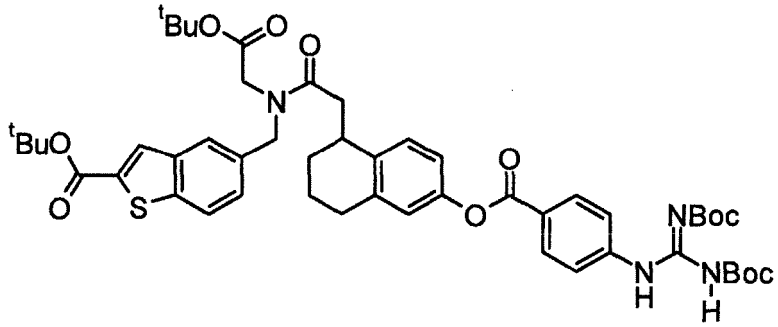
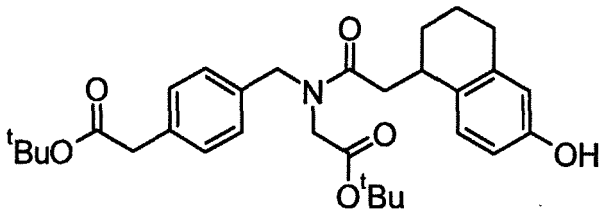
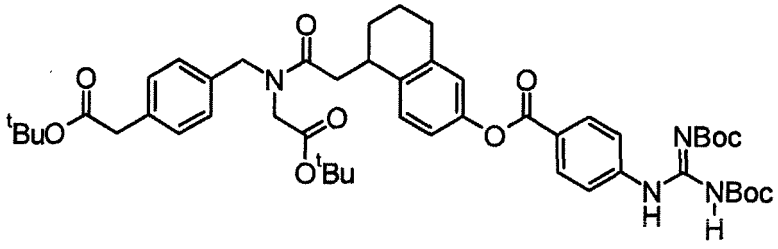
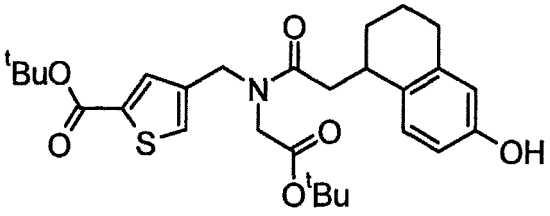
[Table 17]

PEx	PSyn	Str	Data
69	P3		ESI+:873
70	P2		ESI+: 552 [M+Na]+
71	P3		ESI+: 891
72	P6		ESI+: 532 [M+Na]+
73	P3		ESI+: 871

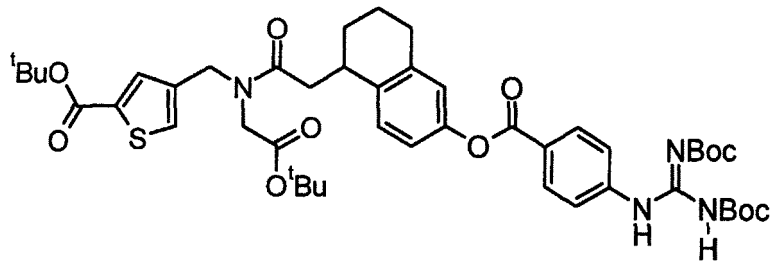
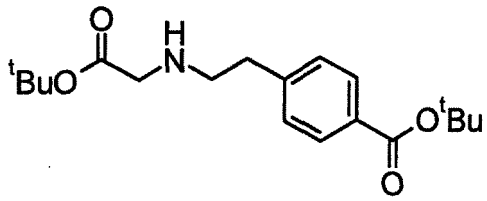
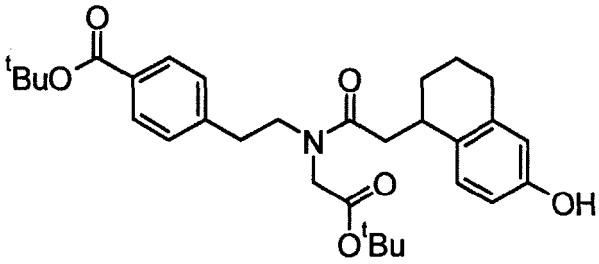
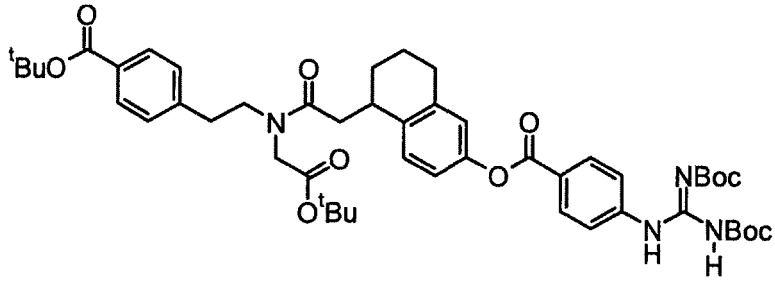
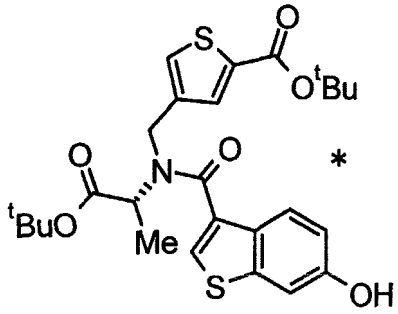
[Table 18]

PEx	PSyn	Str	Data
74	P2		ESI+: 538 [M+Na]+
75	P3		ESI+: 877
76	P3		ESI+: 885
77	P6		ESI+: 552

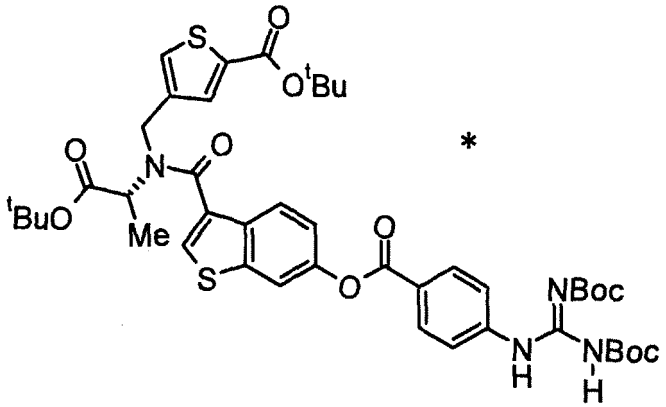
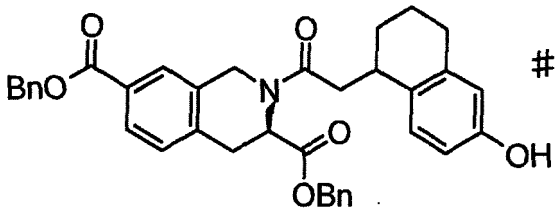
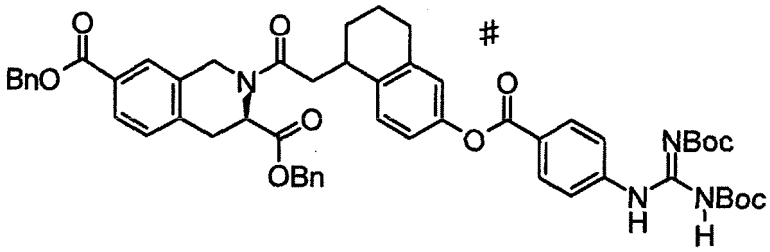
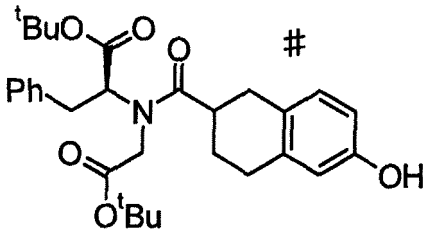
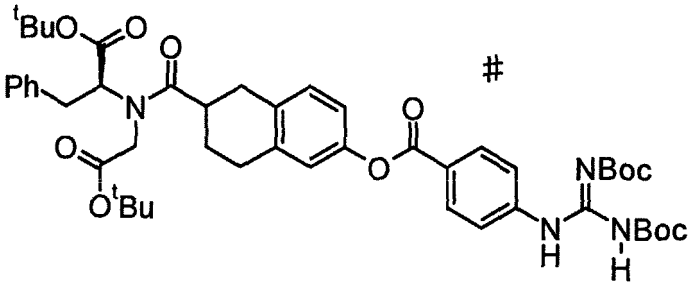
[Table 19]

PEx	PSyn	Str	Data
78	P3		ESI+: 913
79	P6		ESI+: 588 [M+Na]+
80	P3		ESI+:927
81	P6		ESI+: 546 [M+Na]+
82	P3		ESI+: 885
83	P6		ESI+: 538 [M+Na]+

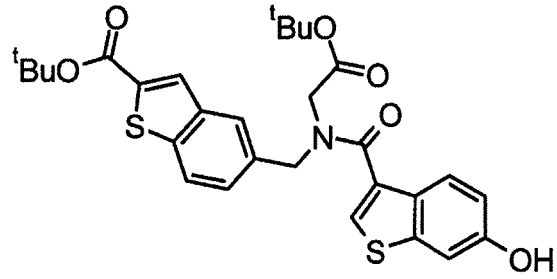
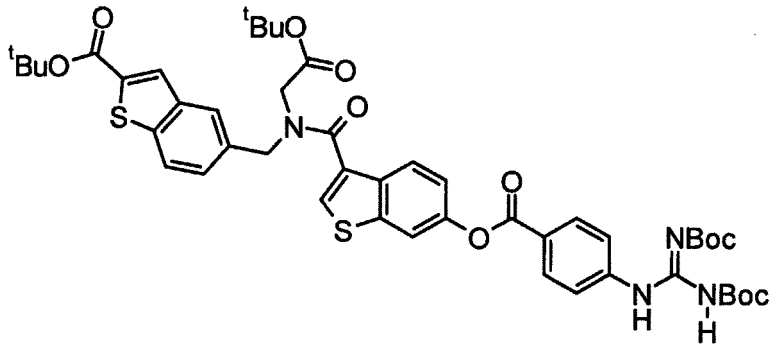
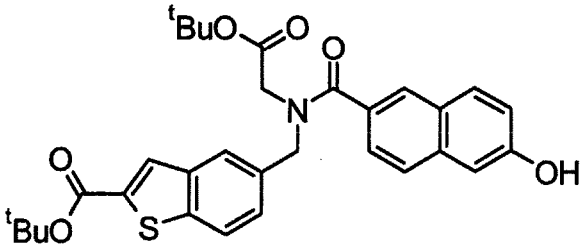
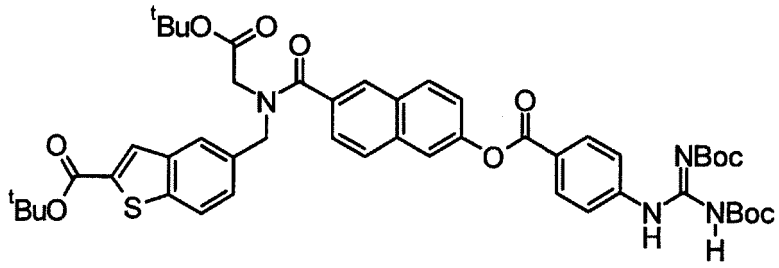
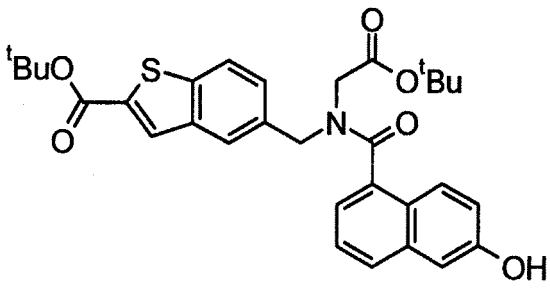
[Table 20]

PEx	PSyn	Str	Data
84	P3		ESI+:877
85	P20		ESI+: 336
86	P6		ESI+: 546 [M+Na]+
87	P3		ESI+: 885
88	P17		ESI+: 540 [M+Na]+

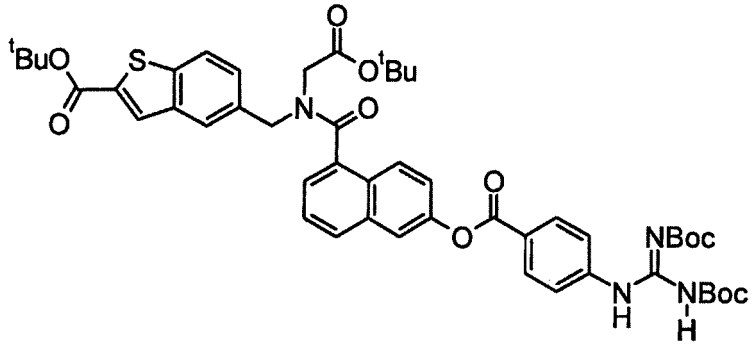
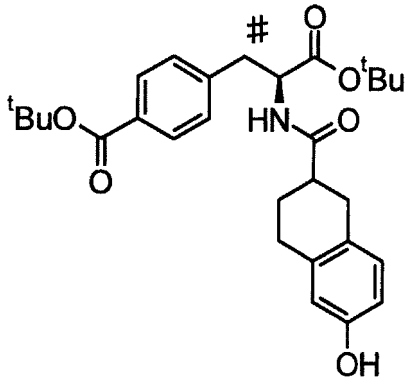
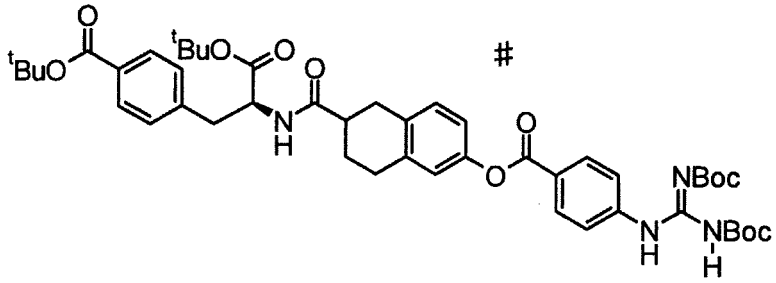
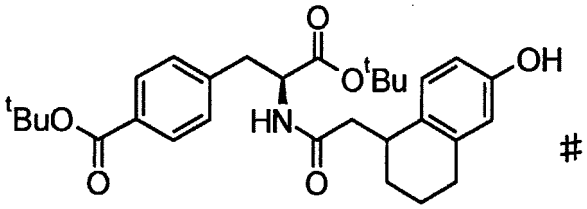
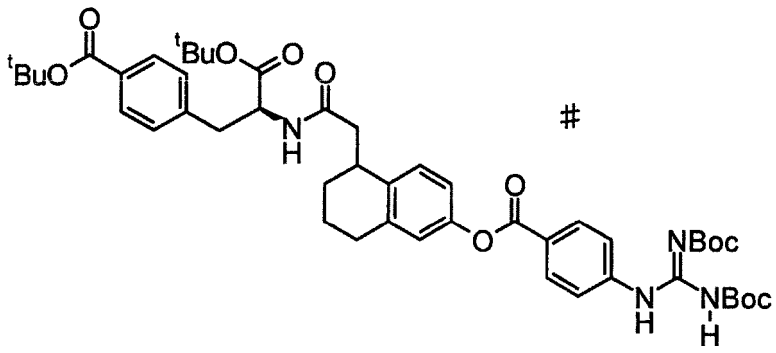
[Table 21]

PEx	PSyn	Str	Data
89	P3		ESI+: 879
90	P6		ESI+: 612 [M+Na]+
91	P3		ESI+: 951
92	P17		ESI+:532 [M+Na]+
93	P3		ESI+: 871

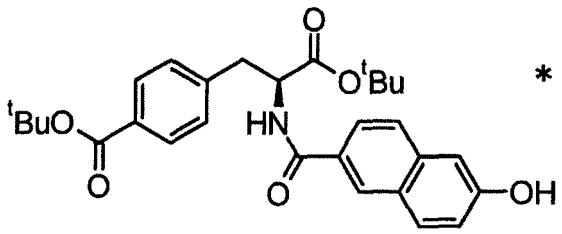
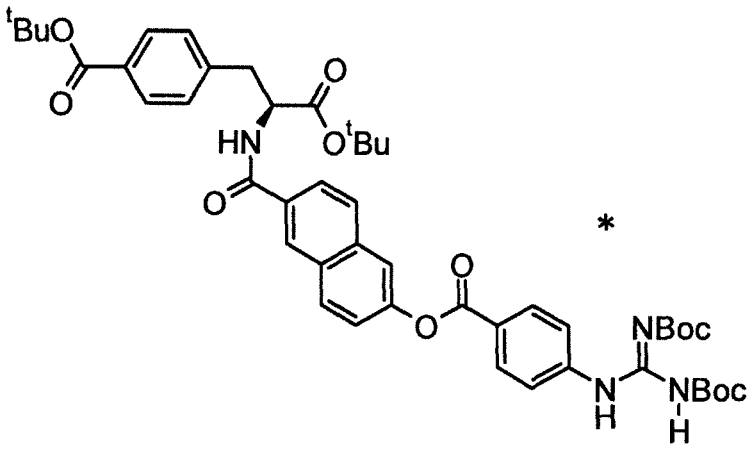
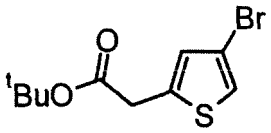
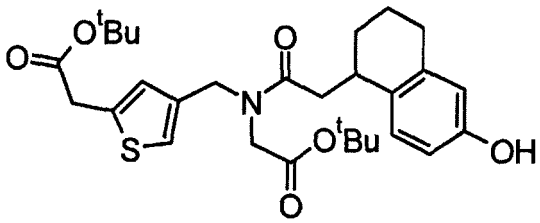
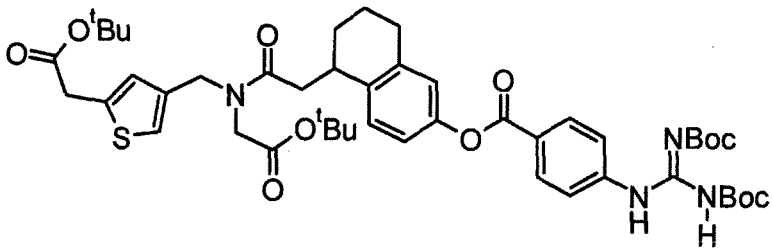
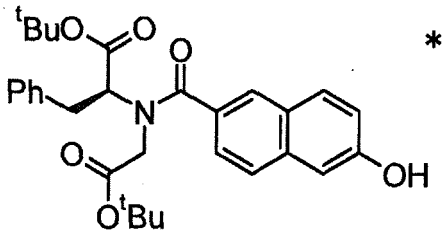
[Table 22]

PEx	PSyn	Str	Data
94	P17		ESI+: 576 [M+Na]+
95	P3		ESI+: 915
96	P6		ESI+: 570 [M+Na]+
97	P3		ESI+: 909
98	P6		ESI+: 570 [M+Na]+

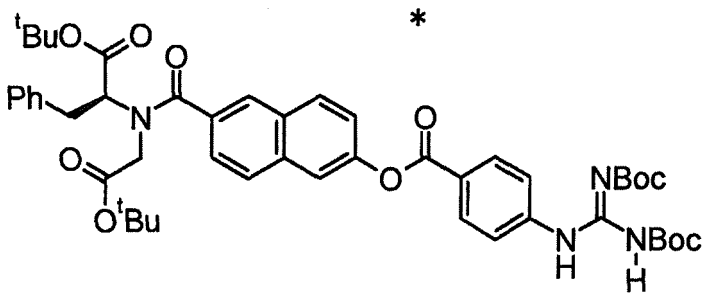
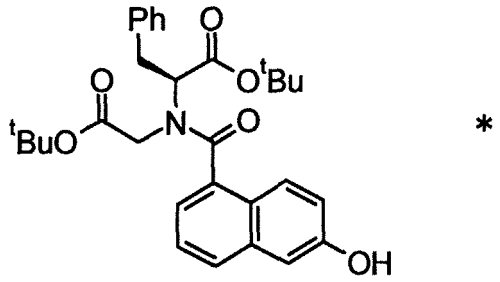
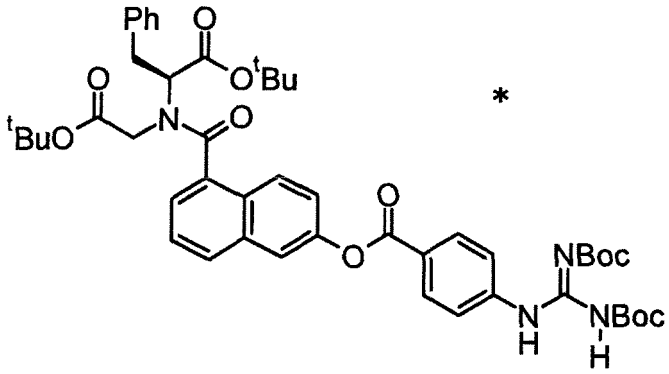
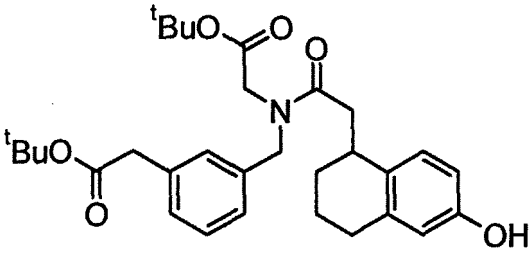
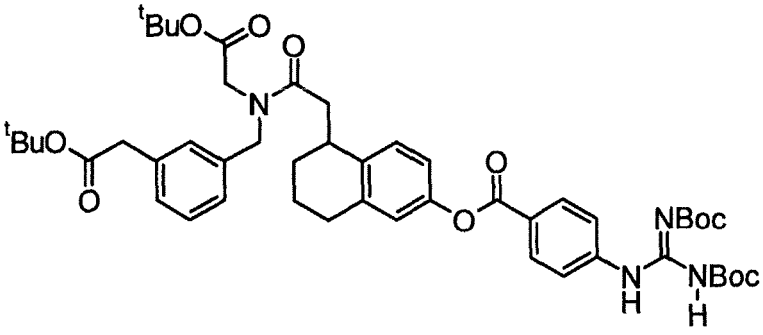
[Table 23]

PEx	PSyn	Str	Data
99	P3		ESI+: 909
100	P6		ESI+: 518 [M+Na]+
101	P3		ESI+: 857
102	P6		ESI+: 532 [M+Na]+
103	P3		ESI+: 871

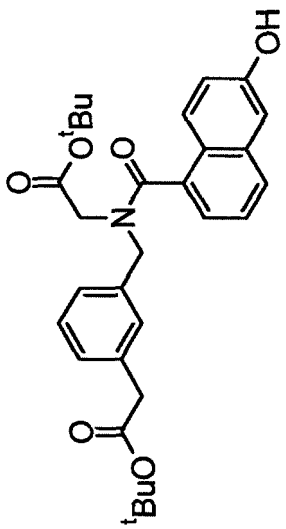
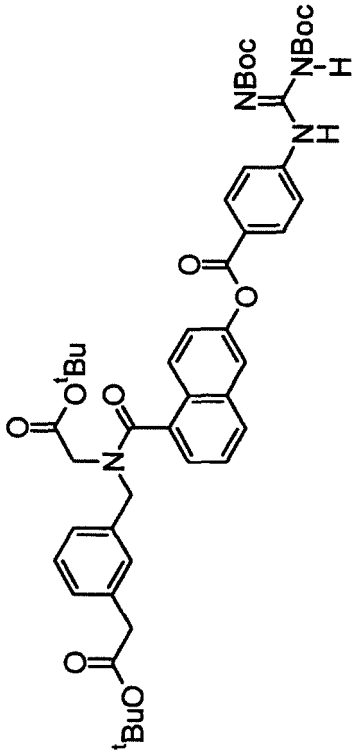
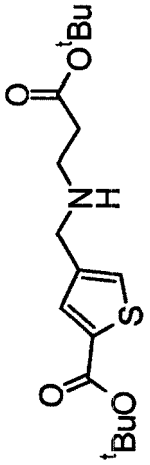
[Table 24]

PEx	PSyn	Str	Data
104	P6		ESI+: 492
105	P3		ESI+: 853
106	P16		ESI+: 299 [M+Na]+
107	P2		ESI+: 552 [M+Na]+
108	P3		ESI+: 891
109	P17		ESI+: 528 [M+Na]+

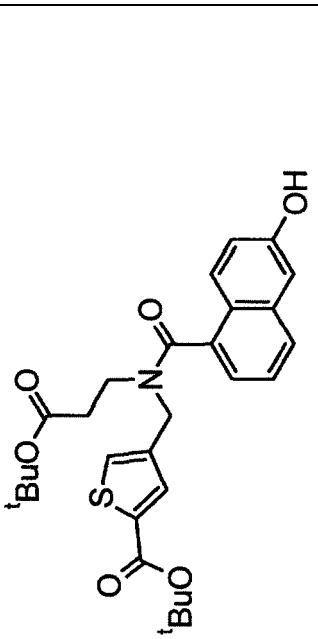
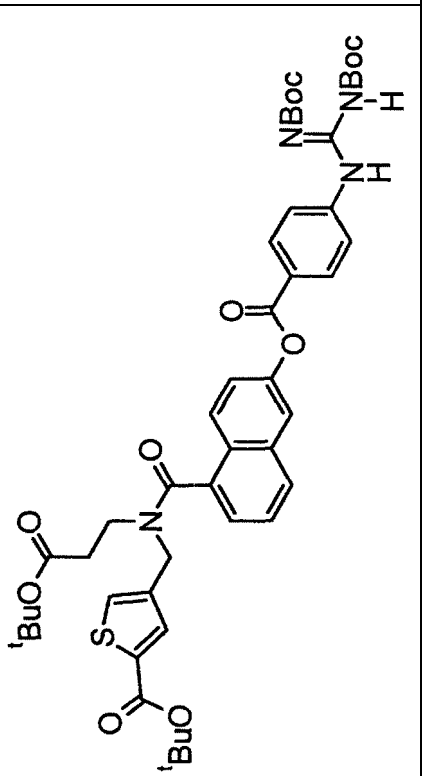
[Table 25]

PEx	PSyn	Str	Data
110	P3		ESI+: 867
111	P17		ESI+: 528 [M+Na]+
112	P3		ESI+:867
113	P6		ESI+:546 [M+Na]+
114	P3		ESI+: 885

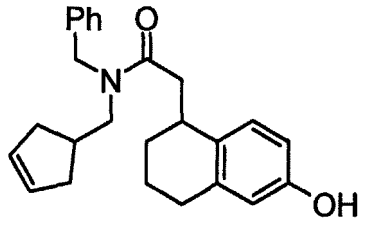
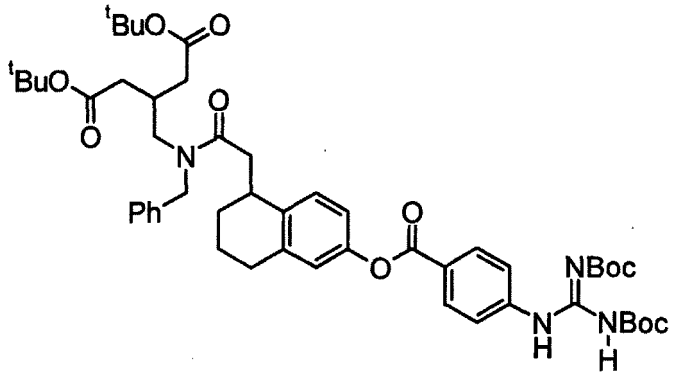
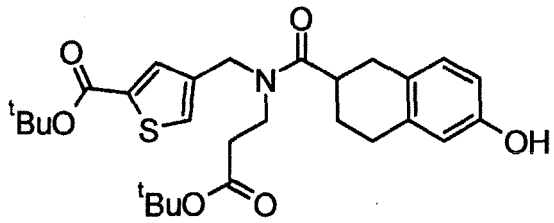
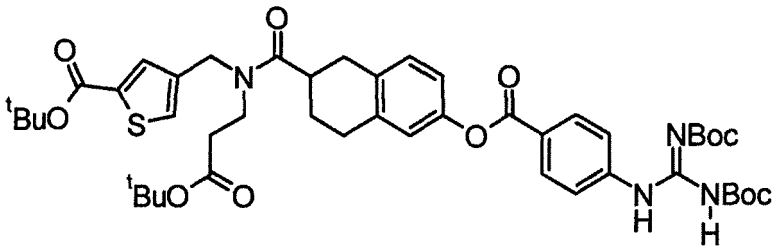
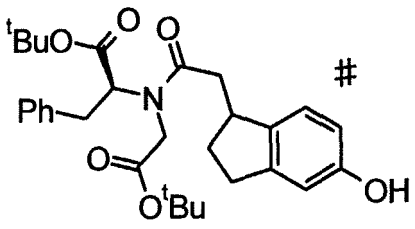
[Table 26]

PEx	PSyn	Str	Data
115	P6		ESI+: 528 [M+Na]+
116	P3		ESI+: 867
117	P1		APCI/ESI+: 342

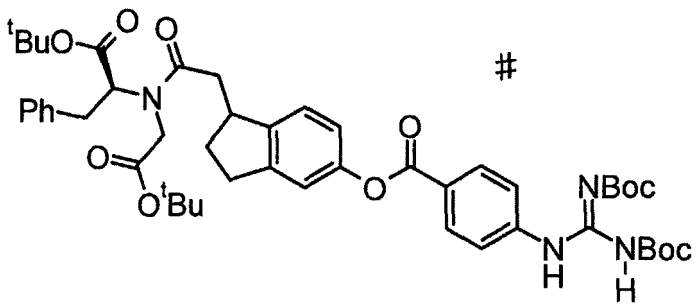
(continued)

PEx	PSyn	Str	Data
118	P17		APCI/ESI+: 512
119	P3		NMR2:1.33-1.65(36H,m),2.25-5.09(6H,m),7.11-7.98(10H,m),8.16-8.26(2H,m),10.66(1H,brs),11.63(1H,brs)

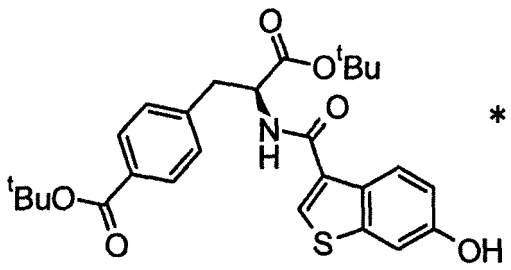
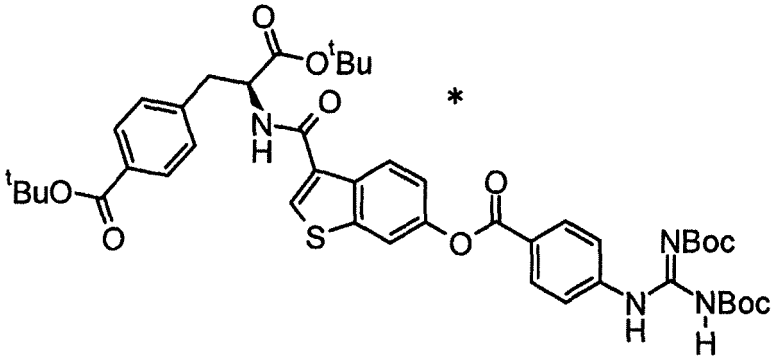
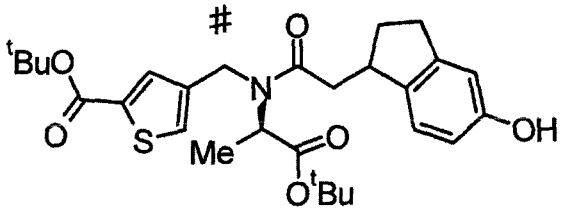
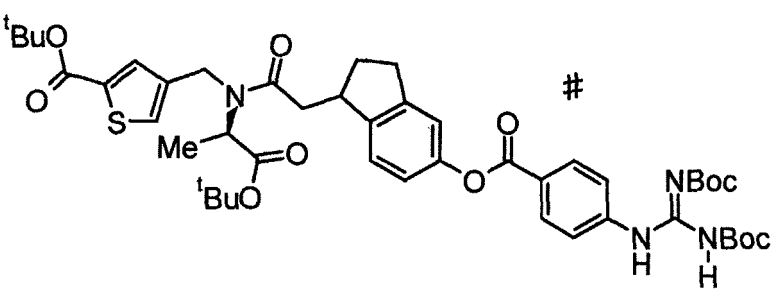
[Table 27]

PEx	PSyn	Str	Data
120	P6		ESI+: 376
121	P3		ESI+: 913
122	P6		ESI+: 538 [M+Na]+
123	P3		ESI+: 877
124	P17		ESI+: 532 [M+Na]+

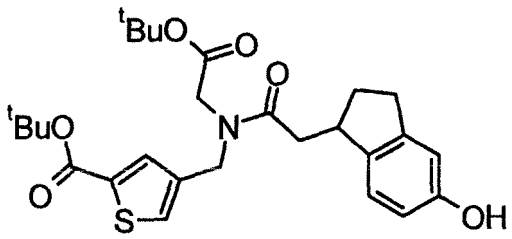
(continued)

PEx	PSyn	Str	Data
125	P3		ESI+: 871

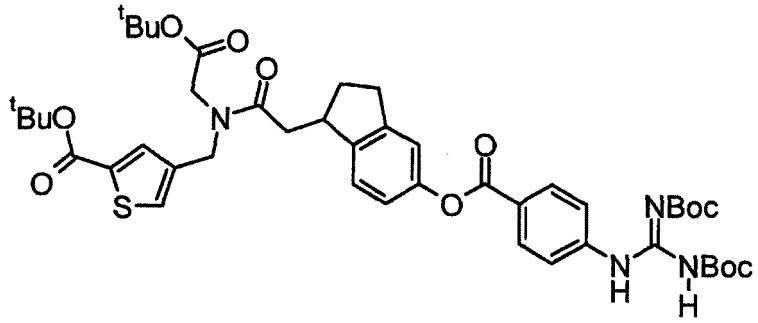
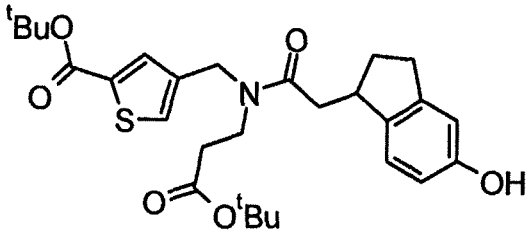
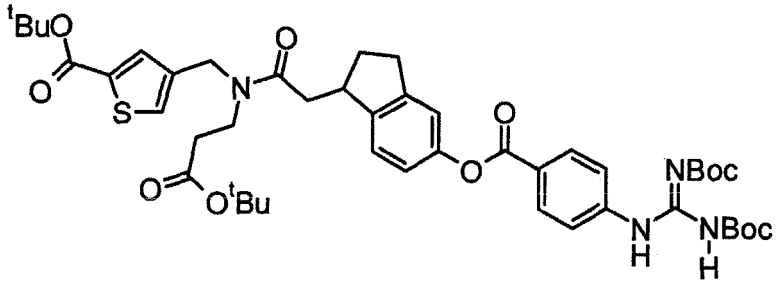
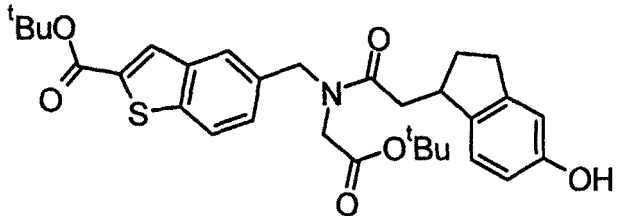
[Table 28]

PEx	PSyn	Str	Data
126	P17		ESI+: 520 [M+Na]+
127	P3		ESI+: 859
128	P6		ESI+: 538 [M+Na]+
129	P3		ESI+: 877

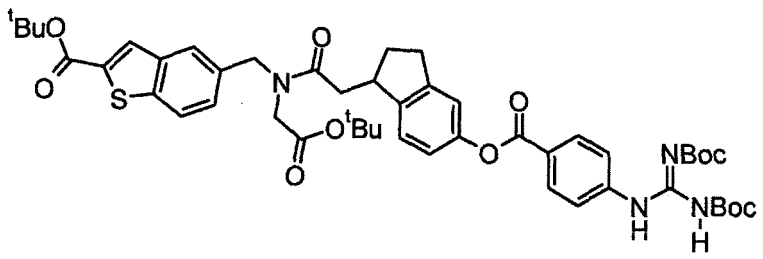
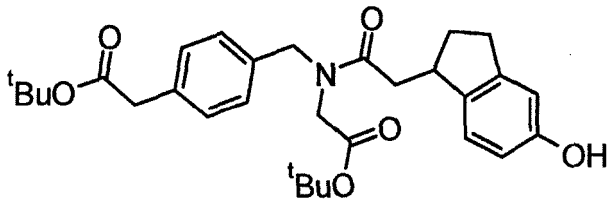
(continued)

PEx	PSyn	Str	Data
130	P6		ESI+: 524 [M+Na]+

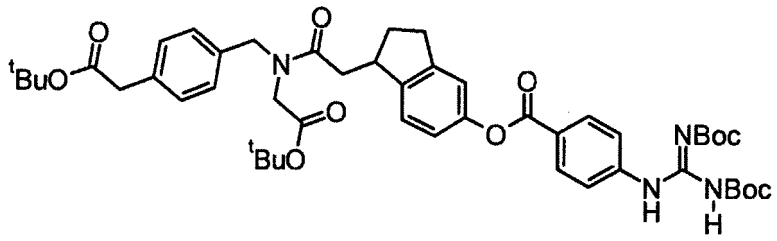
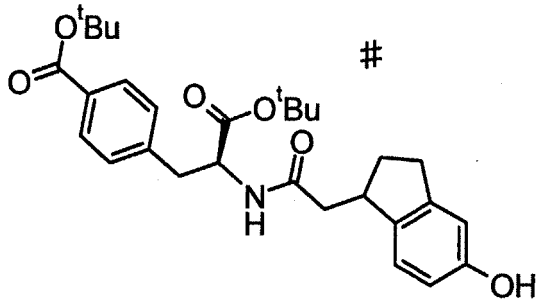
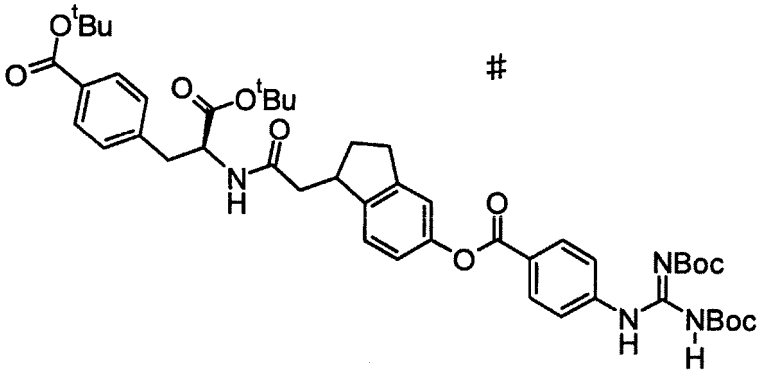
[Table 29]

PEx	PSyn	Str	Data
131	P3		ESI+: 863
132	P6		ESI+: 538 [M+Na]+
133	P3		ESI+:877
134	P6		ESI+: 574 [M+Na]+

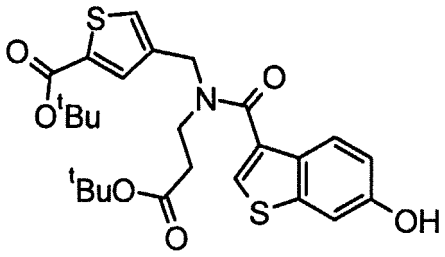
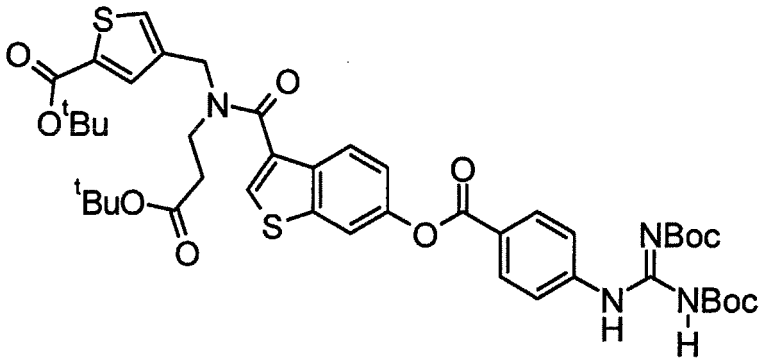
(continued)

PEx	PSyn	Str	Data
135	P3		ESI+: 913
136	P6		ESI+: 532 [M+Na]+

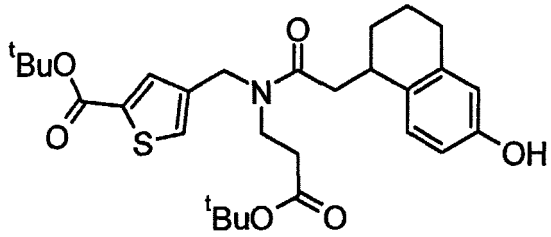
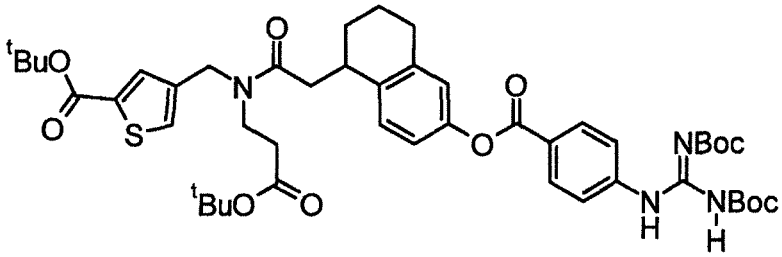
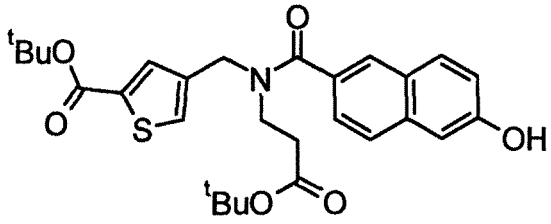
[Table 30]

PEx	PSyn	Str	Data
137	P3		ESI+: 871
138	P6		ESI+: 518 [M+Na]+
139	P3		ESI+: 857

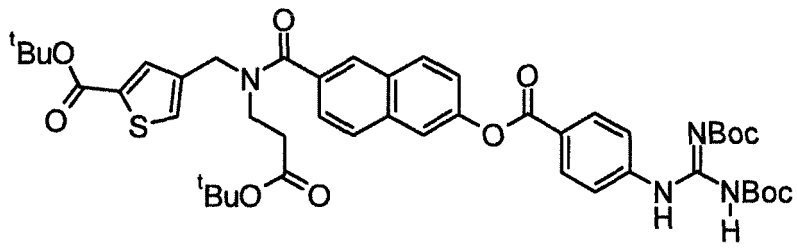
(continued)

PEx	PSyn	Str	Data
140	P17		ESI+: 540 [M+Na]+
141	P3		ESI+: 879

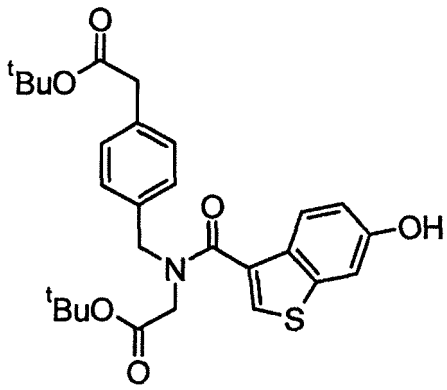
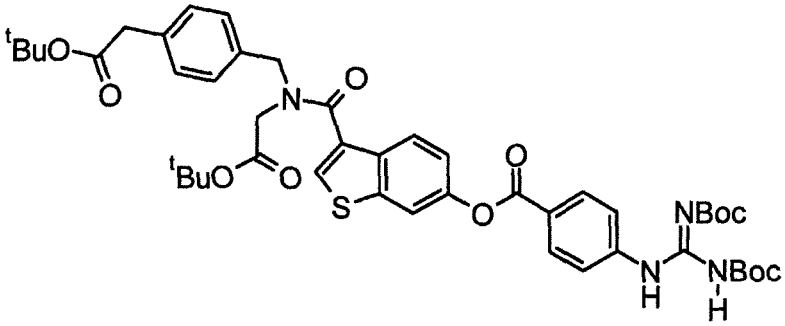
[Table 31]

PEx	PSyn	Str	Data
142	P2		ESI+: 530
143	P3		ESI+: 891
144	P2		ESI+: 534 [M+Na]+

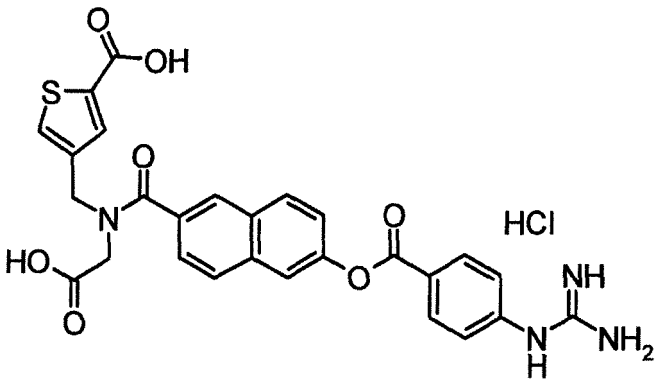
(continued)

PEx	PSyn	Str	Data
145	P3		ESI+: 873

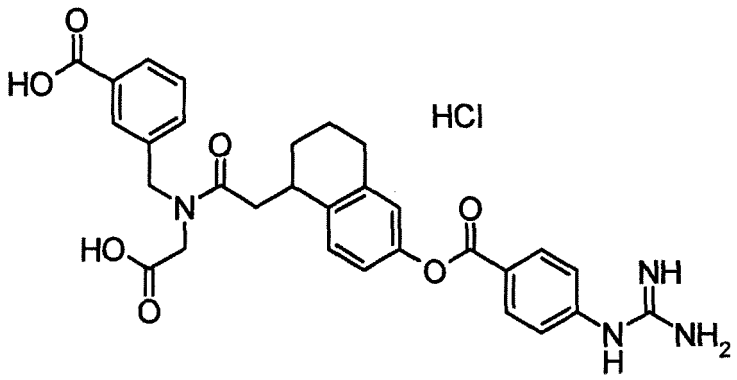
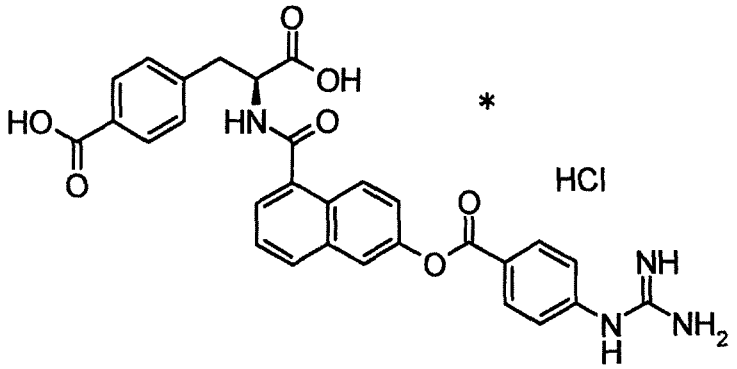
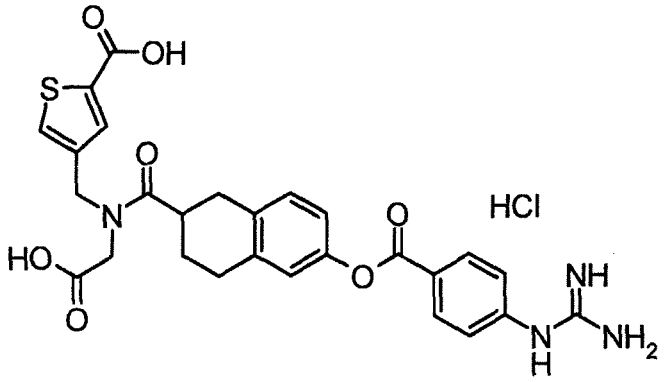
[Table 32]

PEx	PSyn	Str	Data
146	P13		ESI+: 534 [M+Na]+
147	P3		ESI+: 895 [M+Na]+

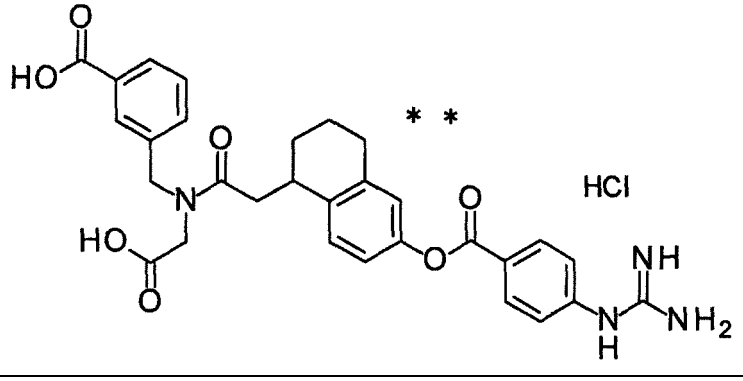
[Table 33]

Ex	Str
1	

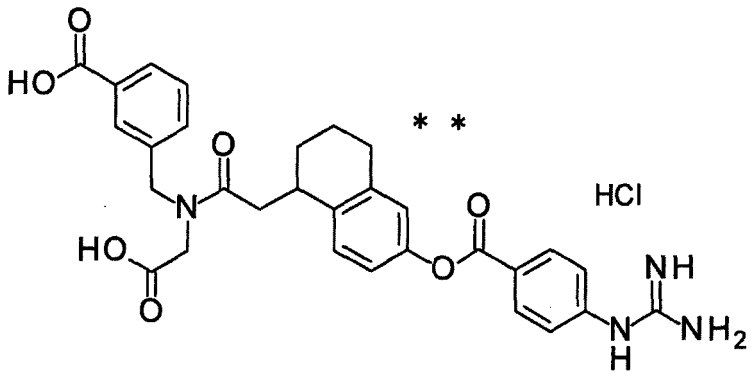
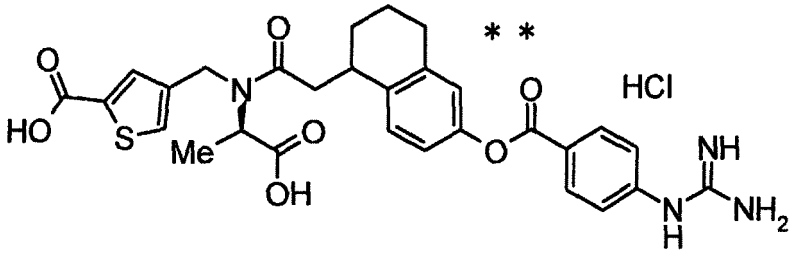
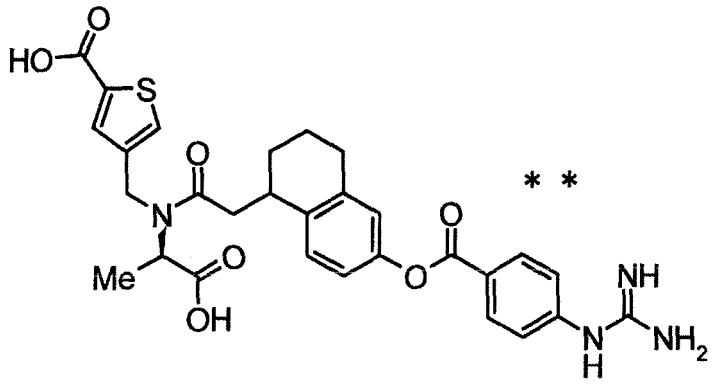
(continued)

Ex	Str
2	
3	
4	

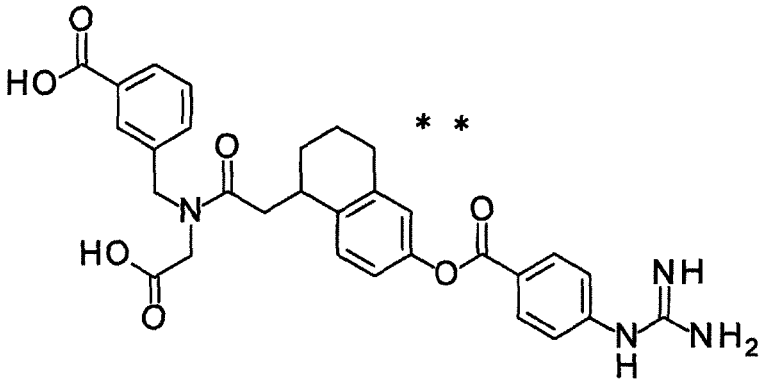
[Table 34]

Ex	Str
5	

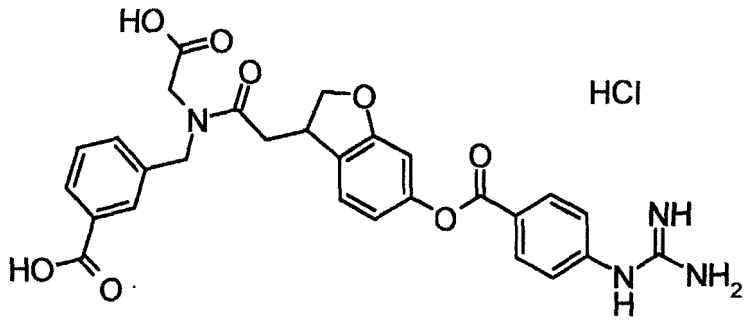
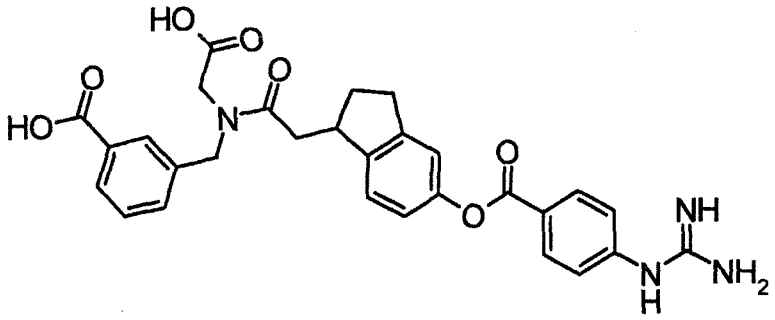
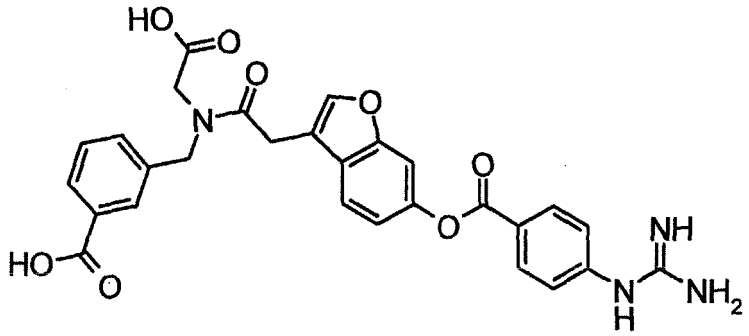
(continued)

Ex	Str
6	
7	
8	

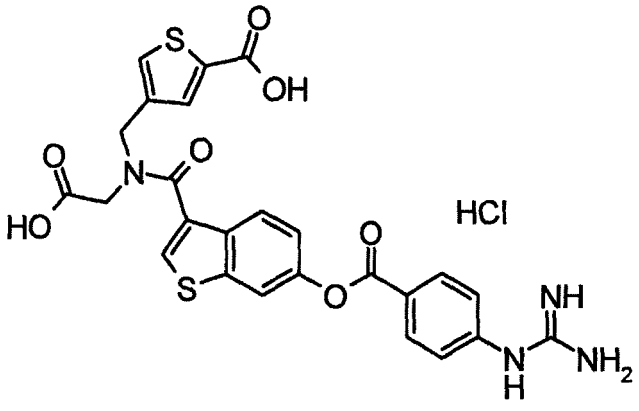
[Table 35]

Ex	Str
9	

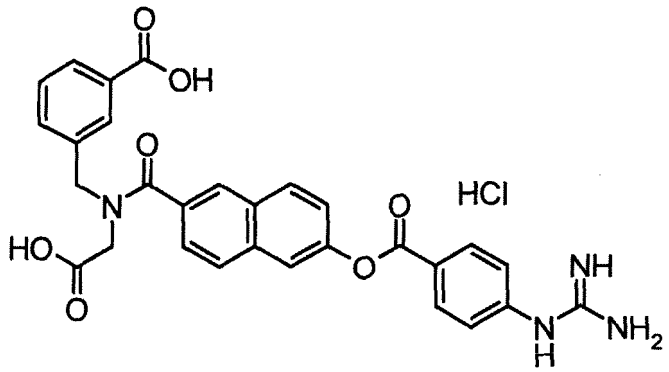
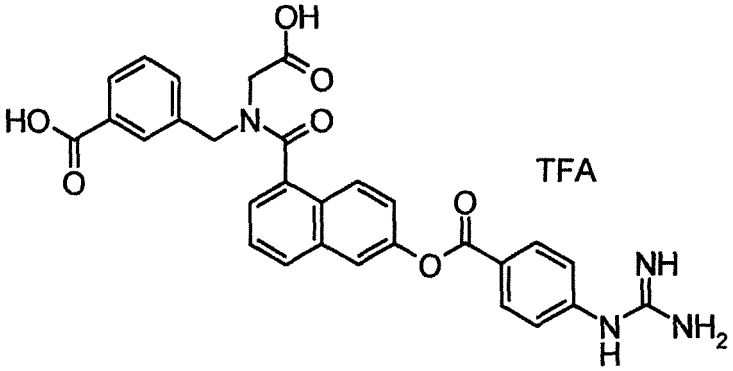
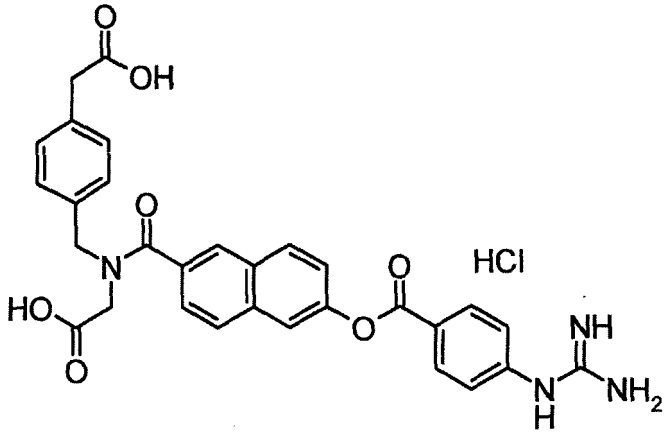
(continued)

Ex	Str
10	
11	
12	

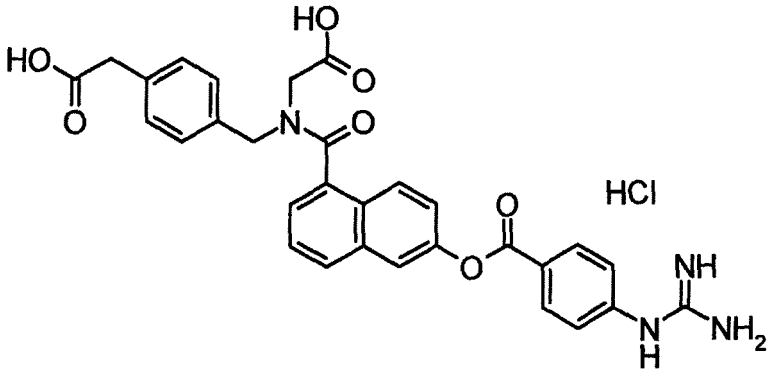
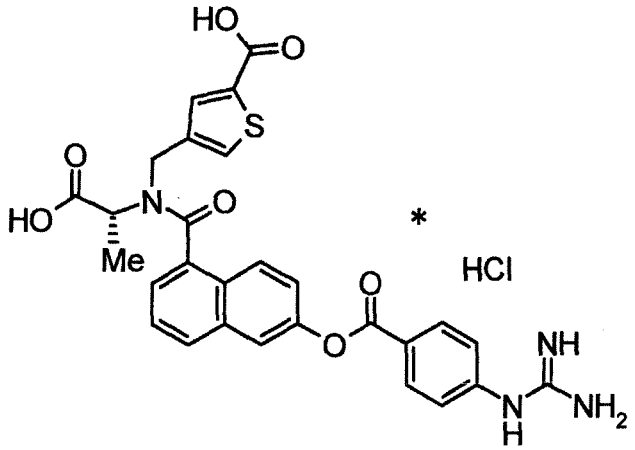
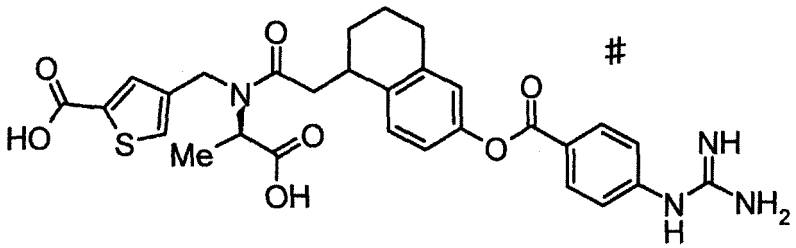
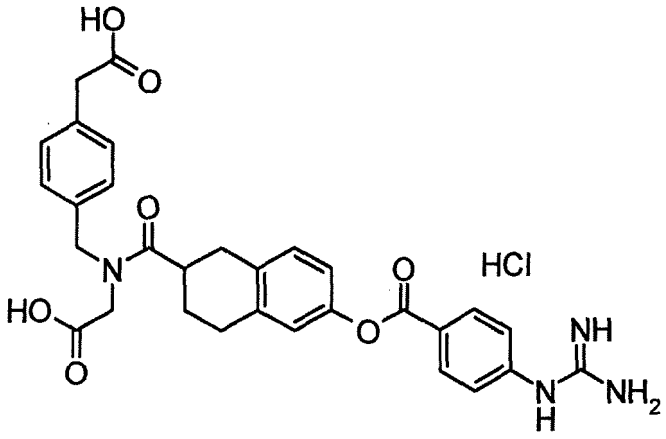
[Table 36]

Ex	Str
13	

(continued)

Ex	Str
14	
15	
16	

[Table 37]

Ex	Str
17	
18	
19	
20	

[Table 38]

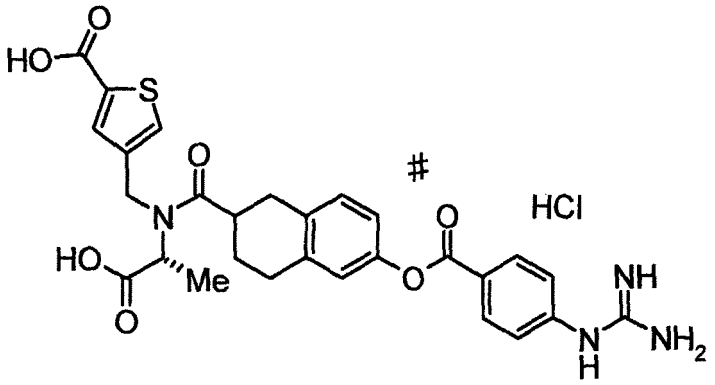
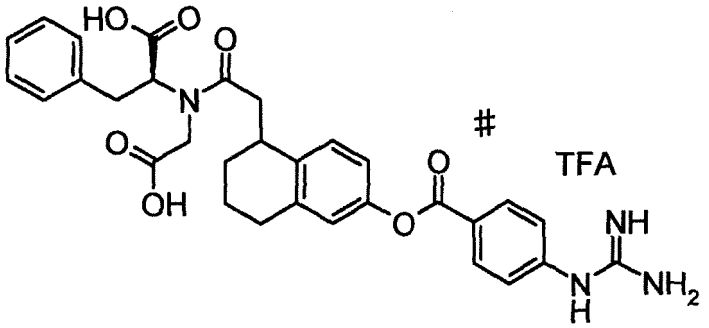
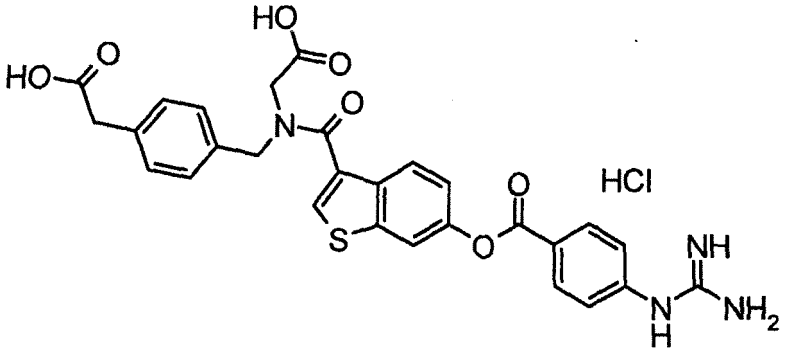
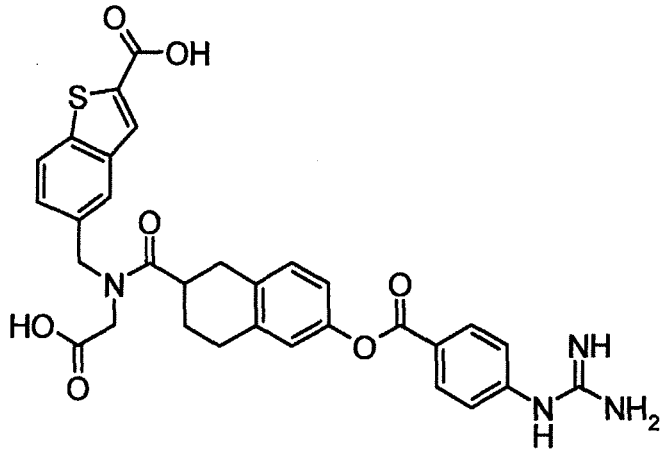
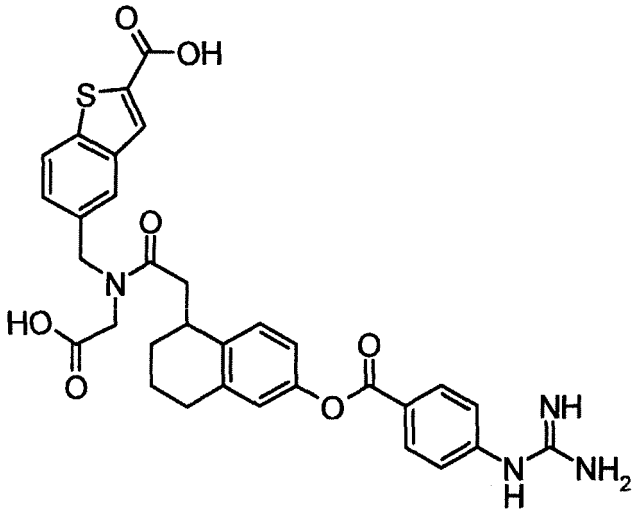
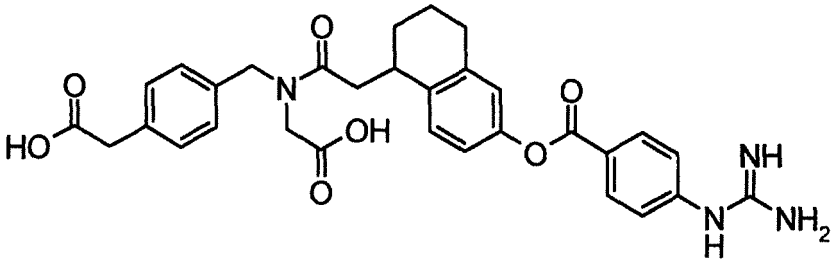
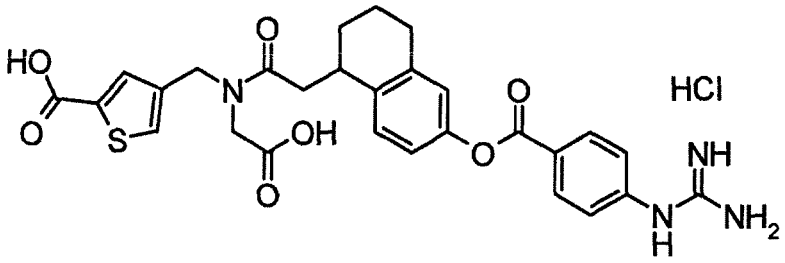
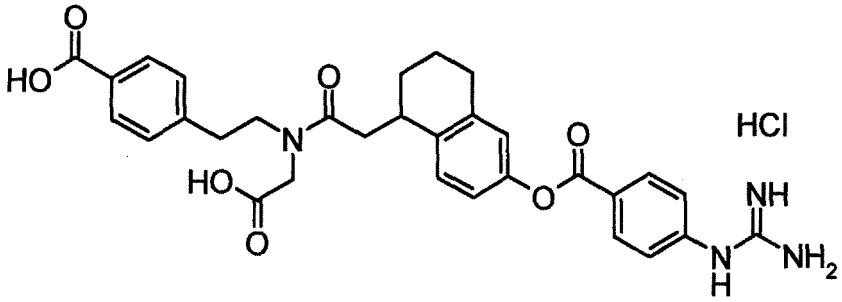
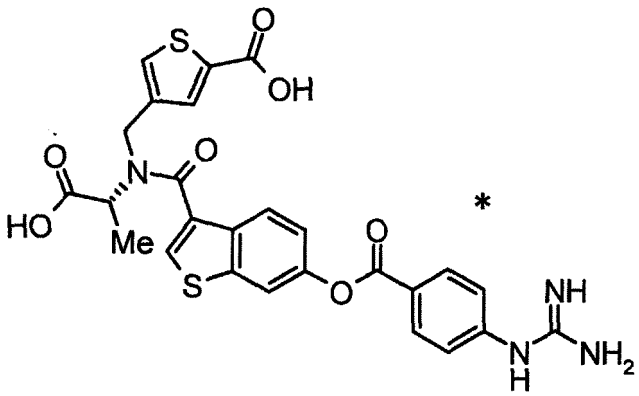
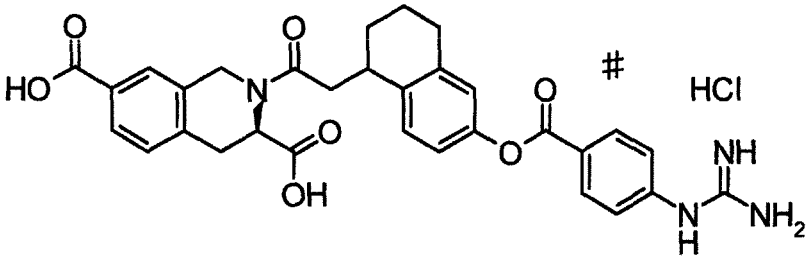
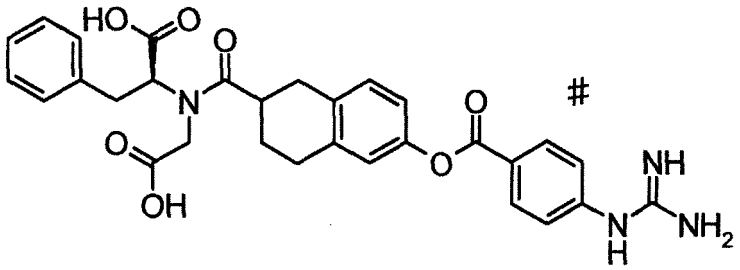
Ex	Str
21	
22	
23	

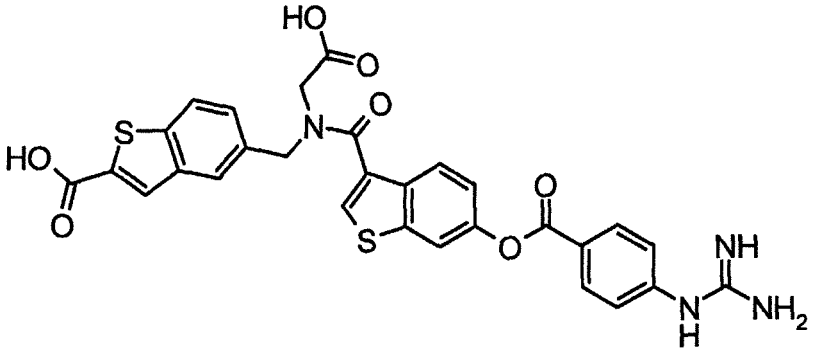
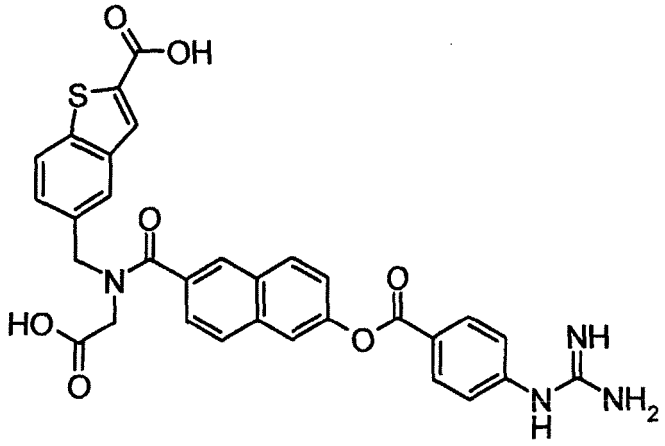
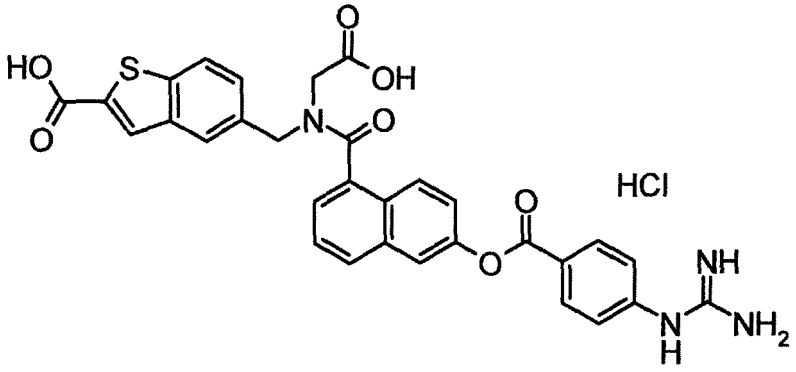
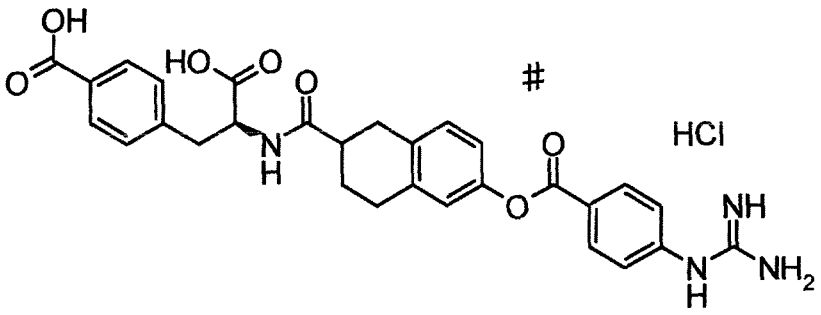
Table 39]

Ex	Str
24	
25	
26	
27	

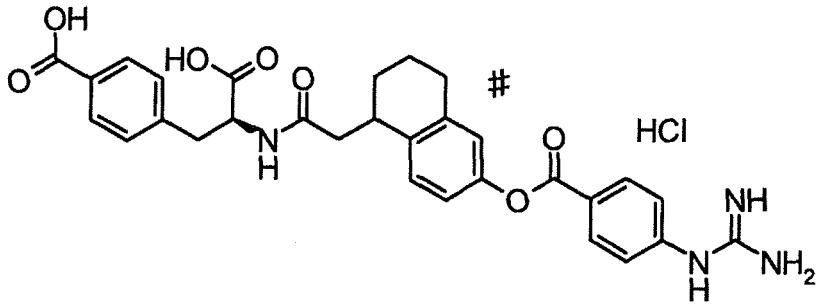
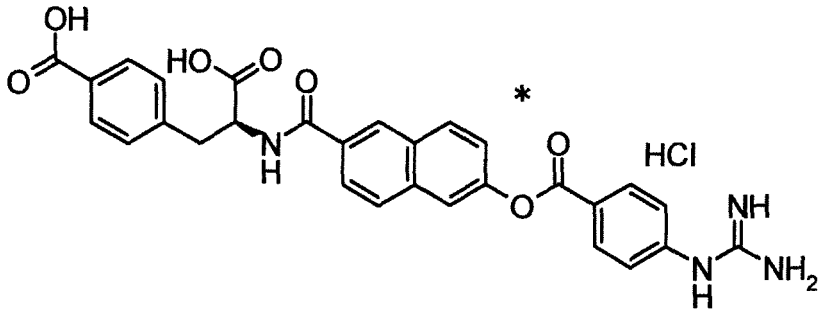
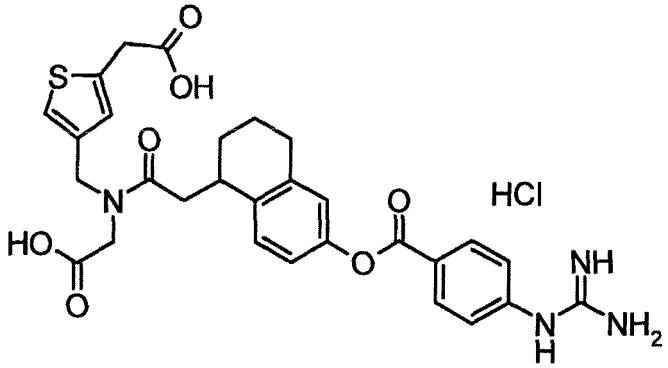
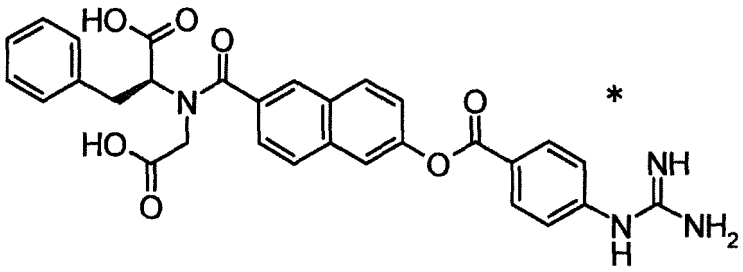
[Table 40]

Ex	Str
28	
29	
30	
31	

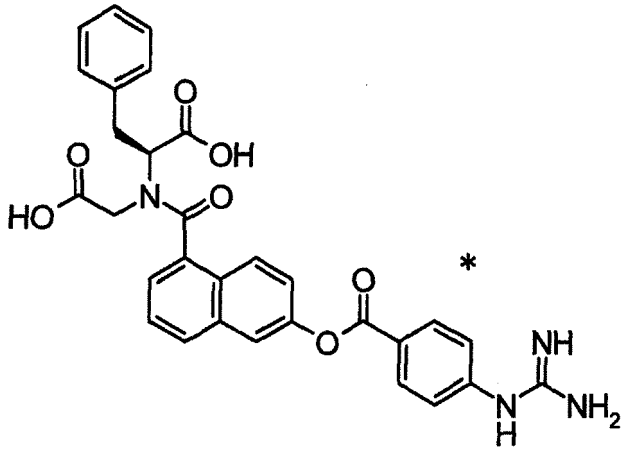
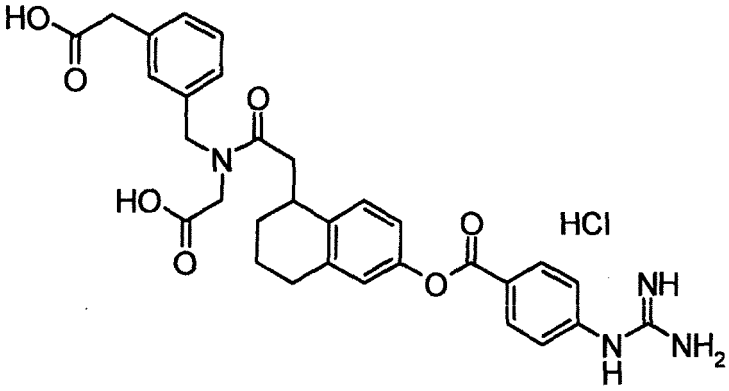
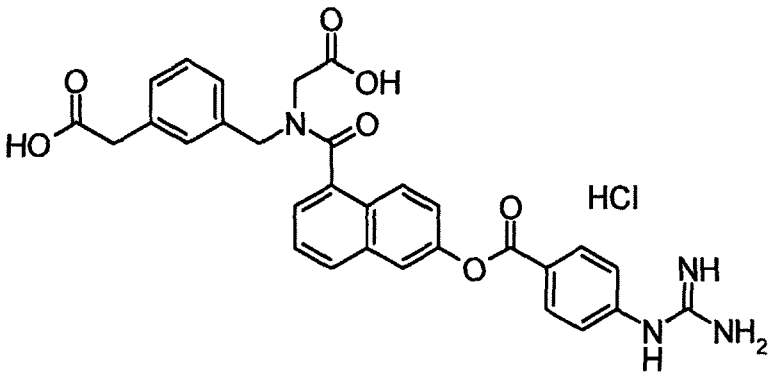
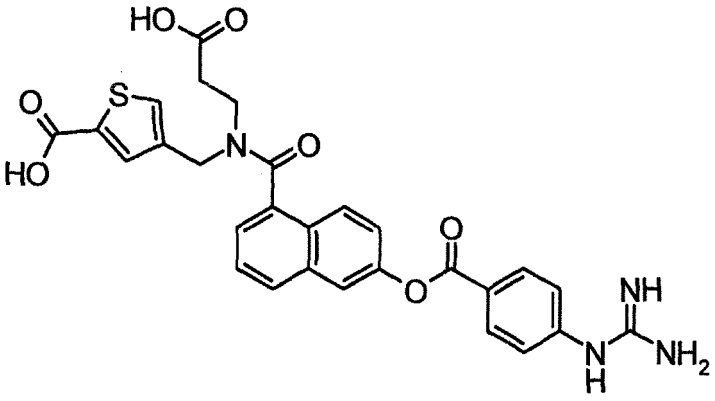
[Table 41]

Ex	Str
32	
33	
34	
35	

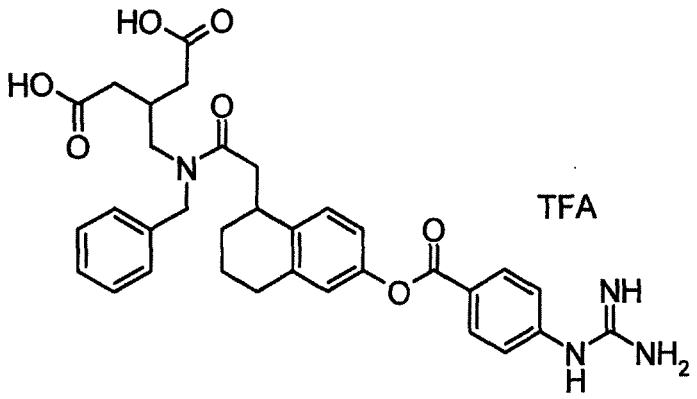
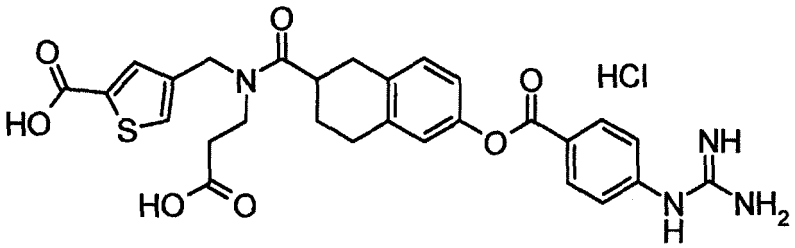
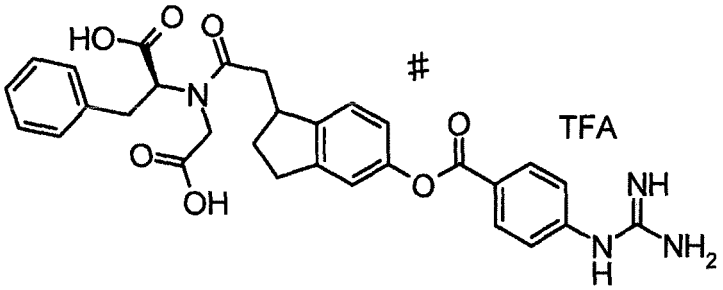
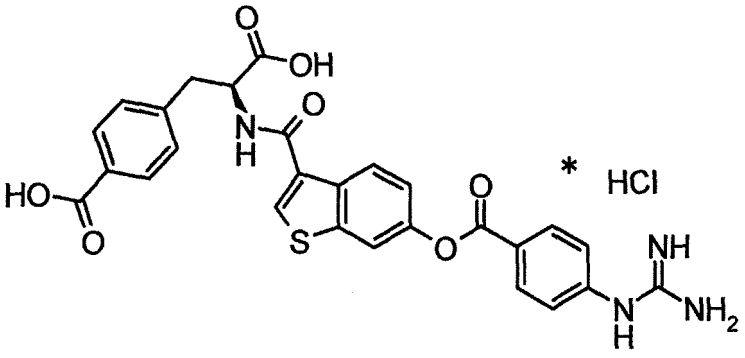
[Table 42]

Ex	Str
36	
37	
38	
39	

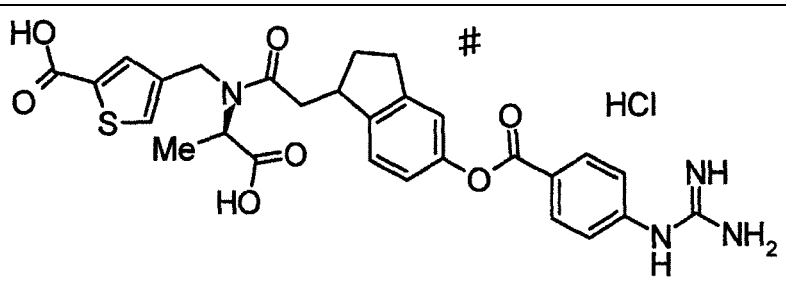
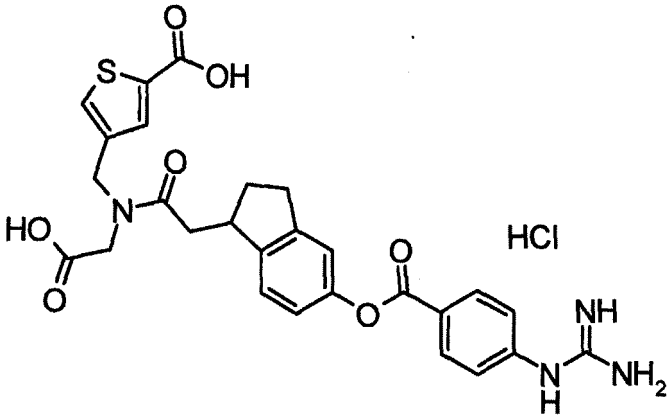
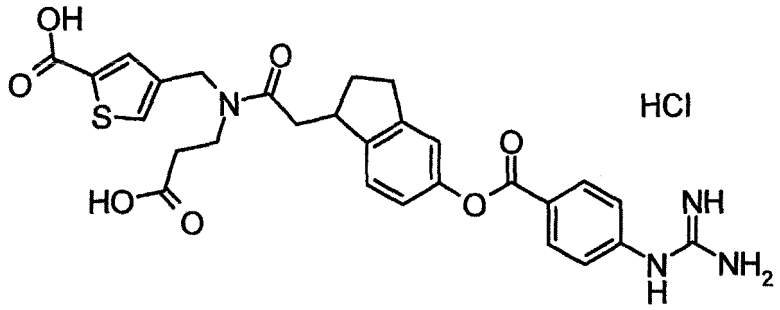
[Table 43]

Ex	Str
40	
41	
42	
43	

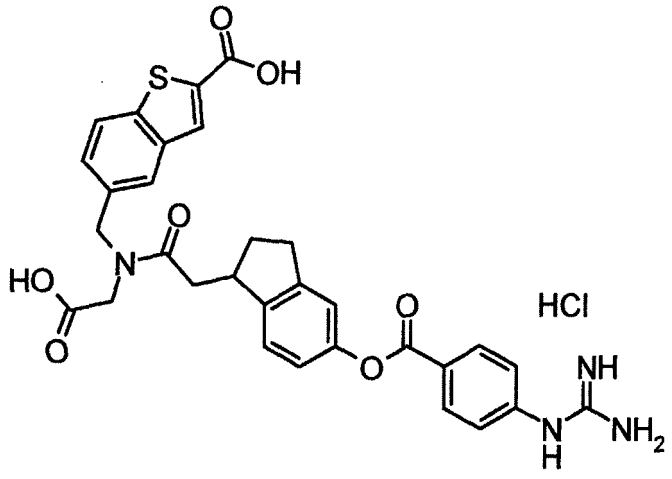
[Table 44]

Ex	Str
44	
45	
46	
47	

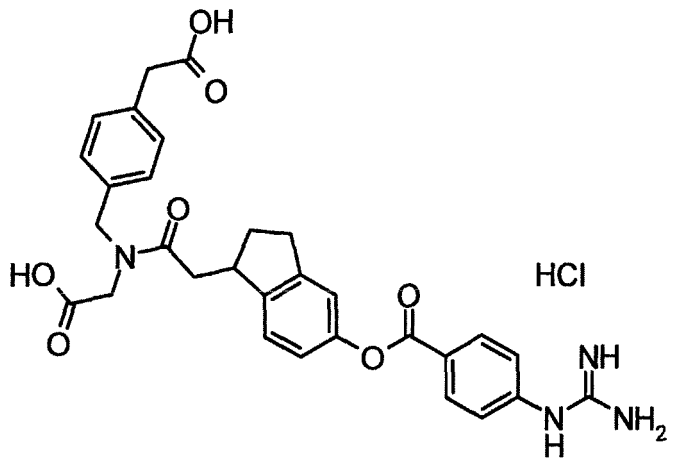
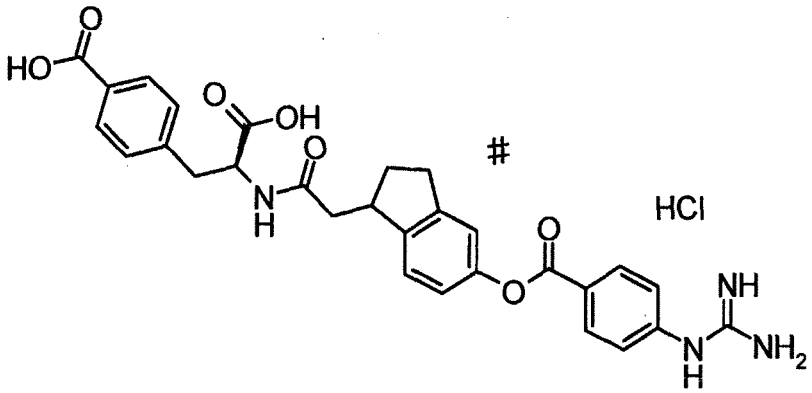
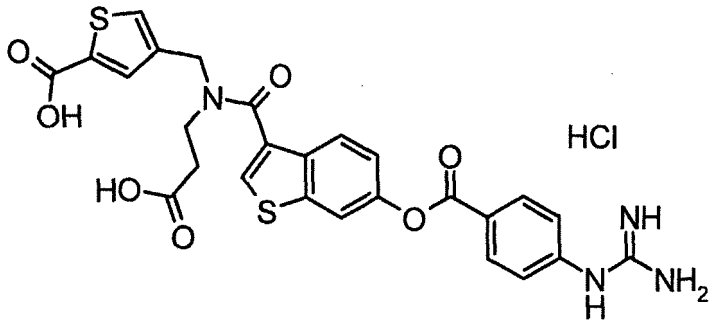
[Table 45]

Ex	Str
48	
49	
50	

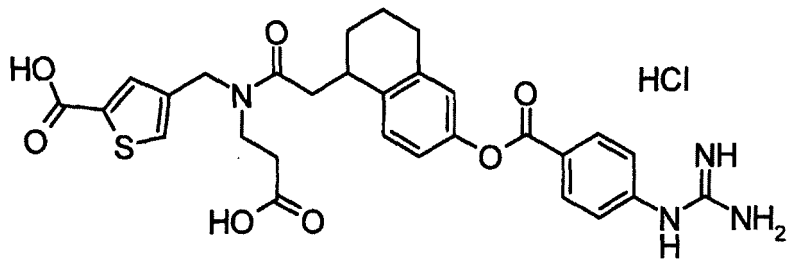
[Table 46]

Ex	Str
51	

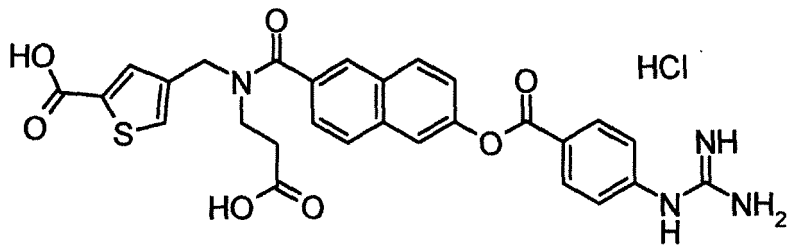
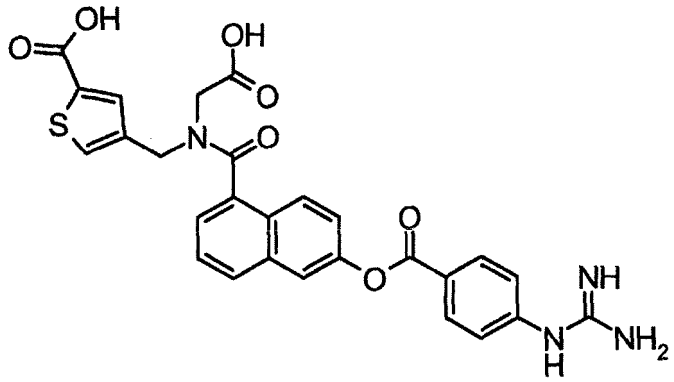
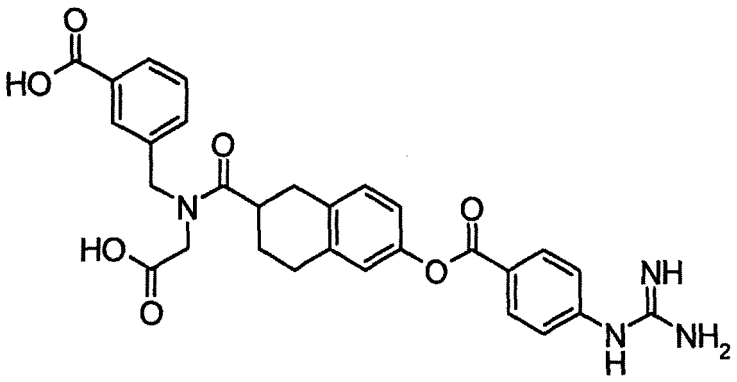
(continued)

Ex	Str
52	
53	
54	

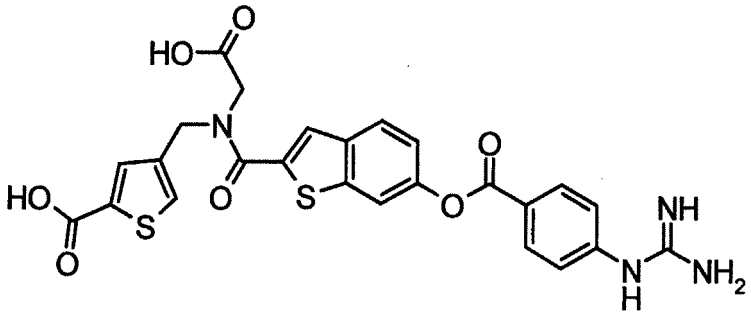
[Table 47]

Ex	Str
55	

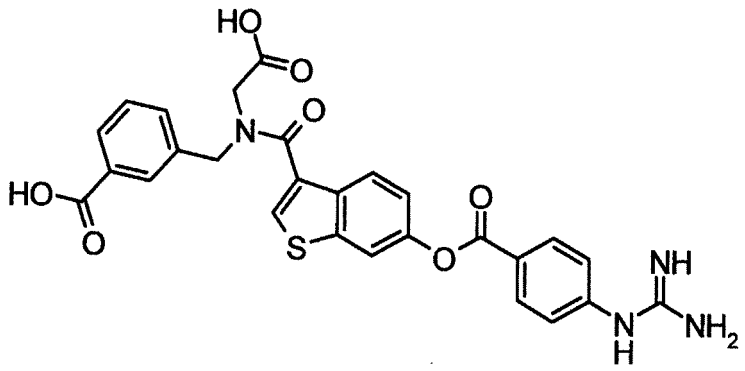
(continued)

Ex	Str
56	
57	
58	

[Table 48]

Ex	Str
59	

(continued)

Ex	Str
60	

[Table 49]

Ex	Syn	Data
1	1	ESI+: 547 NMR1: 4.00 (2H×0.5, brs), 4.13 (2Hx0.5, brs), 4.55 (2H×0.5, brs), 4.69 (2H×0.5, brs), 7.43-7.60 (4H, m), 7.70-7.96 (3H, m), 7.82 (4H, brs), 7.98-8.12 (3H, m), 8.19-8.27 (2H, m), 10.20-10.56 (1H, br), 12.50-13.53 (2H, br)
2	2	ESI+: 559 NMR1: 1.50-1.92 (4H, m), 2.57-2.84 (4H, m), 3.28-3.44 (1H, m), 3.93-4.1.9 (2H, m), 4.57 (1H×0.5, d, J=15.1Hz), 4.65 (1H×0.5, d, J=15.1Hz), 4.69-4.82 (1H, m), 6.87-7.00 (2H, m), 7.23 (1H, dd, J=8.5, 12.4Hz), 7.39-7.57 (4H, m), 7.78-7.94 (6H, m), 8.10-8.17 (2H, m), 10.47 (1H, d, J=3.8Hz), 12.00-13.72 (2H, br)
3	3	ESI+: 541 NMR1: 3.09 (1H, dd, J=11.0, 13.8Hz), 3.27-3.38 (1H, m), 4.75-4.86 (1H, m), 7.37 (1H, dd, J=2.4, 9.2Hz), 7.42-7.51 (5H, m), 7.59 (1H, dd, J=7.1, 8.2Hz), 7.83 (4H, brs), 7.86-7.93 (3H, m), 7.95-8.05 (2H, m), 8.19-8.26 (2H, m), 8.93 (1H, d, J=8.3Hz), 10.20-10.81 (1H, br), 12.62-13.16 (2H, br)
4	4	ESI+: 551 NMR1: 1.58-1.99 (2H, m), 2.71-3.15 (5H, m), 3.93-4.09 (2H×0.5, m), 4.15-4.30 (2Hx0.5, m), 4.50 (2H×0.5, brs), 4.71 (2H×0.5, brs), 6.93-7.01 (2H, m), 7.11-7.21 (1H, m), 7.39-7.46 (2H, m), 7.59-7.85 (2H, m), 7.78 (4H, brs), 8.10-8.17 (2H, m), 10.32 (1H, brs), 11.77-14.23 (2H, br)
5	5	ESI+: 559 NMR1: 1.48-1.90 (4H, m), 2.55-2.84 (4H, m), 3.30-3.41 (1H, m), 3.95-4.21 (2H, m), 4.57 (1H×0.5, d, J=15.1Hz), 4.65 (1H×0.5, d, J=15.1Hz), 4.69-4.82 (1H, m), 6.88-7.00 (2H, m), 7.23 (1H, dd, J=8.5, 12.4Hz), 7.38-7.58 (4H, m), 7.74-7.92 (6H, m), 8.08-8.18 (2H, m), 10.41 (1H, d, J=3.8Hz), 12.10-13.81 (2H, br)
6	6	ESI+: 559 NMR1: 1.50-1.92 (4H, m), 2.55-2.84 (4H, m), 3.34-3.44 (1H, m), 3.93-4.18 (2H, m), 4.57 (1H×0.5, d, J=15.1Hz), 4.65 (1H×0.5, d, J=15.1Hz), 4.69-4.82 (1H, m), 6.87-7.00 (2H, m), 7.23 (1H, dd, J=8.5, 12.2Hz), 7.36-7.56 (4H, m), 7.74-7.91 (6H, m), 8.08-8.17 (2H, m), 10.43 (1H, brs), 12.86 (2H, brs)
7	7	ESI+: 579
8	8	ESI+: 579

[Table 50]

Ex	Syn	Data
9	9	ESI+: 559 NMR1: 1.50-1.88 (4H, m), 2.53-2.73 (4H, m), 2.90-3.54 (1H, m), 3.55-3.70 (2H×0.4, m), 3.76-4.07 (2H×0.6, m), 4.43 (2Hx0.4, d, J=15.2Hz), 4.60-4.90 (2H×0.6, m), 6.60-6.70 (2H×0.4, m), 6.80-6.91 (2H×0.6, m), 7.10-7.28 (1H, m), 7.30-7.52 (4H, m), 7.77-7.88 (2H, m), 8.07 (2H, d, J=8.6Hz), 8.17-8.80 (4H, br), 12.20-13.60 (2H, br)
10	2	ESI+: 547

(continued)

Ex	Syn	Data
11	2	ESI+: 545 NMR1: 1.59-1.78 (1H, m), 2.24-2.40 (1H, m), 2.44-2.59 (1H, m), 2.65-2.90 (3H, m), 3.49-3.62 (1H, m), 3.70-4.10 (2H, m), 4.50-4.85 (2H, m), 6.77-6.85 (1H×0.7, m), 6.86-6.93 (1H×0.3, m), 6.98-7.05 (1H, m), 7.13-7.54 (5H, m), 7.79-7.89 (2H, m), 7.96-8.40 (6H, m), 11.02-13.60 (2H, br)
12	2	ESI+: 545
13	2	ESI+: 553 NMR1: 4.08-4.20 (2H, m), 4.53 (2H×0.5, brs), 4.72 (2H×0.5, brs), 7.33-7.43 (1H, m), 7.43-7.49 (2H, m), 7.50-8.09 (5H, m), 7.80 (4H, brs), 8.17-8.23 (2H, m), 10.31 (1H, s), 12.62-13.35 (2H, m)
14	2	ESI+: 541
15	2	ESI+: 541 NMR1: 3.53-5.19 (4H, m), 7.37-8.31 (14H, m), 7.83 (4H, brs), 10.33 (1H, s), 12.37-13.46 (2H, br)
16	2	ESI+: 555
17	2	ESI+: 555 NMR1: 3.20-5.04 (6H, m), 7.04-8.30 (14H, m), 7.83 (4H, brs), 10.39 (1H, s), 11.72-13.46 (2H, br)
18	2	ESI+: 561
19	2	ESI+: 579 NMR1: 1.19-1.36 (3H, m), 1.38-1.88 (4H, m), 2.31-2.81 (4H, m), 3.20-3.40 (1H, m), 4.08-4.86 (3H, m), 6.82-6.98 (2H, m), 7.12-7.30 (1H, m), 7.34-7.59 (4H, m), 7.97-8.40 (2H, m), 8.18 (4H, brs), 11.30-13.63 (2H, br)
20	2	ESI+: 559
21	2	ESI+: 565 NMR1: 1.22-1.41 (3H, m), 1.58-2.02 (2H, m), 2.56-3.12 (5H, m), 4.10-4.97 (3H, m), 6.90-7.04 (2H, m), 7.08-7.24 (1H, m), 7.38-7.48 (2H, m), 7.55-7.94 (2H, m), 7.79 (4H, brs), 8.08-8.19 (2H, m), 10.33 (1H, s), 12.15-13.48 (2H, br)
22	2	ESI+: 573

[Table 51]

Ex	Syn	Data
23	2	ESI+: 561 NMR1:3.49-3.90(4H,m),4.36(2H×0.67,brs),4.76(2H×0.33,brs),6.66-7.58(7H,m),7.70-8.73(9H,m),11.93-14.29(2H,m)
24	2	ESI+: 601
25	2	ESI+: 615
26	2	ESI+: 573
27	2	ESI+: 565
28	2	ESI+: 573
29	2	ESI+: 567
30	2	ESI+: 571
31	2	ESI+: 559
32	2	ESI+: 603
33	2	ESI+: 597
34	2	ESI+: 597
35	2	ESI+: 545
36	2	ESI+: 559
37	2	ESI+: 541
38	2	ESI+: 579
39	2	ESI+: 555
40	2	ESI+: 555
41	2	ESI+: 573
42	2	ESI+: 555
43	2	ESI+: 561
44	2	ESI+:601
45	2	ESI+: 565
46	2	ESI+: 559
47	2	ESI+: 547

(continued)

Ex	Syn	Data
48	2	ESI+: 565
49	2	ESI+: 551
50	2	ESI+: 565
51	2	ESI+: 601
52	2	ESI+: 559
53	2	ESI+: 545
54	2	ESI+: 567
55	2	ESI+: 579
56	2	ESI+: 561
57	2	ESI+: 547
58	2	ESI+: 545
59	1	ESI+: 553
60	2	ESI+: 547

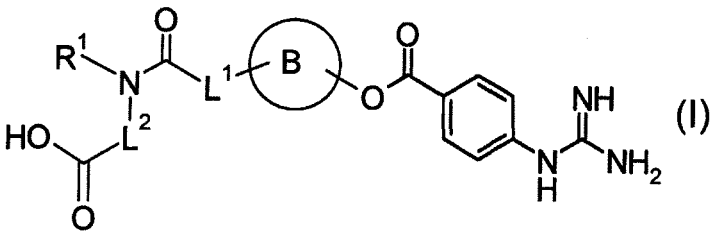
Industrial applicability

[0143] The compound of Formula (I) or a salt thereof has a trypsin inhibitory action, and therefore, can be used as an agent for preventing and/or treating kidney diseases as an agent which will substitute low-protein diet therapy, and/or an agent for preventing and/or treating trypsin-related diseases such as chronic pancreatitis, gastroesophageal reflux disease, hepatic encephalopathy, and influenza.

Claims

1. A compound of Formula (I) or a salt thereof:

[Chem. 9]



(I)

(in which

L^1 is a bond or -lower alkylene-,
L^2 is lower alkylene which may be substituted,
R^1 is lower alkyl which may be substituted with a substituent selected from the group consisting of aryl which may be substituted, an aromatic heterocyclic group which may be substituted, and $-CO_2H$, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form cyclic amino which may be substituted with $-CO_2H$, and
Ring B is naphthalenediyl, 1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, benzothiophenediyl, benzofurandiyl, or 2,3-dihydrobenzofurandiyl).

2. The compound or a salt thereof according to claim 1, wherein
L^1 is a bond or C_{1-3} alkylene, L^2 is lower alkylene which may be substituted with a substituent selected from Group D1, and R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) $-CO_2H$, or H, or R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with at least one $-CO_2H$ group,
in which Group D1 includes:

(1) halogen,
(2) -OH and -O-lower alkyl,
(3) -SH and -S-lower alkyl,
(4) -S(O)-lower alkyl and $-S(O)_2$-lower alkyl,
(5) -CN,
(6) $-NO_2$,
(7) $-NH_2$, -NH-(lower alkyl) and $-N(\text{lower alkyl})_2$,
(8) -C(O)-lower alkyl,
(9) aryl substituted with at least one substituent selected from the group consisting of lower alkyl which may be substituted with at least one substituent selected from the group consisting of halogen and $-CO_2H$, -O-(lower alkyl which may be substituted with at least one $-CO_2H$ group), halogen, and $-CO_2H$, and
(10) -C(O)-O-lower alkyl and $-CO_2H$ or a biological equivalent thereof, and

Group D2 includes:

(1) halogen,
(2) -OH and -O-lower alkyl,
(3) -SH and -S-lower alkyl,
(4) -S(O)-lower alkyl and -$S(O)_2$-lower alkyl,
(5) -CN,
(6) -NO_2,
(7) -NH_2, -NH-(lower alkyl), and -N(lower $alkyl)_2$,
(8) -C(O)-lower alkyl,
(9) -C(O)-NH_2, -C(O)-NH-(lower alkyl), and -C(O)-N(lower $alkyl)_2$,
(10) -C(O)-O-lower alkyl and -CO_2H or a biological equivalent thereof, and
(11) lower alkyl and -O-lower alkyl which may be each substituted with at least one substituent selected from the group consisting of (1) to (10) above.

3. The compound or a salt thereof according to claim 1, wherein L^1 is a bond or methylene, L^2 is lower alkylene which may be substituted with a substituent selected from Group D1, R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) aryl which may be substituted with a substituent selected from Group D2, ii) an aromatic heterocyclic group which may be substituted with a substituent selected from Group D2, and iii) -CO_2H, or H, and Ring B is naphthalenediyl, 1,2,3,4-tetrahydronaphthalenediyl, 2,3-dihydroindenediyl, or benzothiophenediyl.

4. The compound or a salt thereof according to claim 3, wherein L^2 is methylene, ethylene, or ethylene substituted with (phenyl substituted with -CO_2H).

5. The compound or a salt thereof according to claim 3, wherein L^2 is methylene, methylmethylene, ethylene, or methylmethylene substituted with (phenyl substituted with -CO_2H).

6. The compound or a salt thereof according to claim 4 or 5, wherein R^1 is lower alkyl which may be substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and iii) -CO_2H, or H.

7. The compound or a salt thereof according to claim 6, wherein Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, or benzothiophene-3,6-diyl.

8. The compound or a salt thereof according to claim 7, wherein L^2 is methylene or methylmethylene, and R^1 is lower alkyl substituted with at least one substituent selected from the group consisting of i) phenyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) thienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, or L^2 is methylmethylene substituted with (phenyl substituted with -CO_2H), and R^1 is H.

9. The compound or a salt thereof according to claim 8, wherein L^2 is methylene or methylmethylene, and R^1 is (phenyl substituted with -CO_2H)-CH_2-, (phenyl substituted with -CH_2-CO_2H)-CH_2-, or (thienyl substituted with -CO_2H)-CH_2-.

10. The compound or a salt thereof according to claim 2, wherein
L^1 is a bond or methylene, Ring B is naphthalene-1,6-diyl, naphthalene-2,6-diyl, 1,2,3,4-tetrahydronaphthalene-1,6-diyl, 1,2,3,4-tetrahydronaphthalene-2,6-diyl, 2,3-dihydroindene-1,5-diyl, benzothiophene-3,6-diyl, benzofuran-3,6-diyl, or 2,3-dihydrobenzofuran-3,6-diyl, and

a) L^2 is C_{1-3} alkylene, and R^1 is lower alkyl which is substituted with at least one substituent selected from the group consisting of i) phenyl which may be substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and ii) an aromatic heterocyclic group selected from thienyl and benzothienyl substituted with at least one substituent selected from the group consisting of -CO_2H and lower alkyl substituted with -CO_2H, and may be substituted with at least one -CO_2H group,
b) L^2 is C_{1-3} alkylene substituted with (phenyl substituted with -CO_2H), and R^1 is H, or
c) R^1 is combined with a nitrogen atom bonded thereto and an HO_2C-L^2 group on the nitrogen atom to form 1,2,3,4-tetrahydroisoquinolin-2-yl substituted with two -CO_2H groups.

11. The compound or a salt thereof according to claim 1, which is

4-{[{6-[(4-carbamimidamidobenzoyl)oxy]-2-naphthoyl}(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
3-{[({(1R)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
3-{[({(1S)-6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
N-{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}-4-carboxy-L-phenylalanine,
4-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}carbonyl)(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[({5-[(4-carbamimidamidobenzoyl)oxy]-2,3-dihydro-1H-inden-1-yl}acetyl)(carboxymethyl)amino]methyl}benzoic acid,
4-{[({6-[(4-carbamimidamidobenzoyl)oxy]-1-benzothiophen-3-yl}carbonyl)(carboxymethyl)amino]methyl}thiophene-2-carboxylic acid,
3-{[{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}(carboxymethyl)amino]methyl}benzoic acid,
N-{6-[(4-carbamimidamidobenzoyl)oxy]-1-naphthoyl}-N-[4-(carboxymethyl)benzyl]glycine,
4-({({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-1-yl}acetyl)[(1R)-1-carboxyethyl]amino}methyl)thiophene-2-carboxylic acid,
4-({({6-[(4-carbamimidamidobenzoyl)oxy]-1,2,3,4-tetrahydronaphthalen-2-yl}carbonyl)[(1R)-1-carboxyethyl]amino}methyl)thiophene-2-carboxylie acid, or
N-({6-[(4-carbamimidamidobenzoyl)oxy]-1-benzothiophen-3-yl}carbonyl)-N-[4-(carboxymethyl)benzyl]glycine.

12. A pharmaceutical composition comprising the compound or a salt thereof according to claim 1, and a pharmaceutically acceptable excipient.

13. The pharmaceutical composition according to claim 12, which is a pharmaceutical composition for preventing or treating kidney diseases.

14. Use of the compound or a salt thereof according to claim 1 for the manufacture of a pharmaceutical composition for preventing or treating kidney diseases.

15. Use of the compound or a salt thereof according to claim 1 for preventing or treating kidney diseases.

16. The compound or a salt thereof according to claim 1 for preventing or treating kidney diseases.

17. A method for preventing or treating kidney diseases, comprising administering an effective amount of the compound or a salt thereof according to claim 1 to a subject.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2014/056601

A. CLASSIFICATION OF SUBJECT MATTER
C07C279/18(2006.01)i, *A61K31/24*(2006.01)i, *A61K31/343*(2006.01)i, *A61K31/381*(2006.01)i, *A61K31/472*(2006.01)i, *A61P13/12*(2006.01)i, *C07D217/26*(2006.01)i, *C07D307/80*(2006.01)i, *C07D333/40*(2006.01)i,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C279/18, A61K31/24, A61K31/343, A61K31/381, A61K31/472, A61P13/12, C07D217/26, C07D307/80, C07D333/40, C07D333/68, C07D333/70

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2014
Kokai Jitsuyo Shinan Koho 1971-2014 Toroku Jitsuyo Shinan Koho 1994-2014

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus/REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 9-124571 A (Japan Tobacco Inc.), 13 May 1997 (13.05.1997), claims; paragraphs [0050] to [0052], [0074], [0456]; compound 14 (Family: none)	1-7,12-14,16
A	WO 2011/071048 A1 (Ajinomoto Co., Inc.), 16 June 2011 (16.06.2011), claims; formula (I); paragraphs [0001], [0039], [0045] & US 2012/0283222 A1 & EP 2511271 A1 & CN 102822154 A	1-14,16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May, 2014 (14.05.14)	27 May, 2014 (27.05.14)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2014/056601

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/37969 A1 (Ono Pharmaceutical Co., Ltd.), 16 October 1997 (16.10.1997), claims; compound 4 & US 6388122 B1 & EP 893437 A1 & KR 10-2000-0005312 A	1-14,16
A	JP 57-53454 A (Torii Pharmaceutical Co., Ltd.), 30 March 1982 (30.03.1982), claims; formula (I) & US 4454338 A & US 4532255 A & GB 2083818 A & EP 48433 A2	1-14,16
A	JP 52-89640 A (Ono Pharmaceutical Co., Ltd.), 27 July 1977 (27.07.1977), claims (Family: none)	1-14,16

Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2014/056601

Continuation of A. CLASSIFICATION OF SUBJECT MATTER
(International Patent Classification (IPC))

C07D333/68(2006.01)i, *C07D333/70*(2006.01)i

(According to International Patent Classification (IPC) or to both national classification and IPC)

Form PCT/ISA/210 (extra sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2014/056601

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15,17
because they relate to subject matter not required to be searched by this Authority, namely:
(See extra sheet)

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2014/056601

Continuation of Box No.II-1 of continuation of first sheet(2)

Claims 15 and 17 pertain to methods for treatment of the human body or animal body by surgery or therapy and thus relate to a subject matter on which this International Searching Authority is not required to carry out an international search under the provisions of PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

Form PCT/ISA/210 (extra sheet) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

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- WO 1991018869 A **[0009]**
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- WO 2011071048 A **[0009]**
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